

American Heart Journal

Vol. 34

JULY, 1947

No. 1

Original Communications

OBSERVATIONS ON CHANGES IN VENTRICULAR COMPLEXES PRODUCED BY BUNDLE BRANCH BLOCK WITH SPECIAL REFERENCE TO THE HYPOTHESIS OF ELECTRICAL AXIS AND THE CONCEPT OF DEXTROCARDIOGRAM AND LEVOCARDIOGRAM

CHARLES C. WOLFERTH, M.D., AND MARY M. LIVEZEY, M.D.
PHILADELPHIA, PA.

WE HAVE previously reported results of electrocardiographic experiments that cast doubt on the validity of some of the underlying assumptions essential to the formulation of Einthoven's classic equilateral triangle hypothesis.¹⁻⁴ Moreover, results obtained by the method of balanced potentials and by placing the reference electrode over the spine of the right scapula led us to conclude that certain parts of the left ventricle tend to exert a greater influence in shaping the ventricular complexes of limb leads than other parts of the ventricular myocardium. As a matter of fact it would be difficult to avoid that conclusion even without special methods of pairing electrodes, provided one merely observes the effects of infarction in various parts of the left ventricle upon supposed electrical axis. Such observations must inevitably lead one to question the hypothesis of electrical axis as it is applied to the interpretation of electrocardiograms. The method of balanced potentials is the only procedure for which there is experimental evidence that the objective of reducing interference with the potential variations of the exploring electrode can be achieved in electrocardiograms; therefore the error involved in using this method to study distribution of potential on body surfaces should be less than that of other methods. It is desirable, nevertheless, to study the problem of electrical axis by some procedure that does not involve a matter still so controversial as the merit of methods of pairing electrodes.

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

Received for publication Sept. 3, 1946.

2

It occurred to us that analysis of the changes that occur in ventricular complexes as a result of human bundle branch block might offer an opportunity to test current views regarding electrical axis and Lewis' views regarding the human dextrocardiogram and levocardiogram, which he developed on the basis of his studies of canine bundle branch block, and which he tried to explain on the basis of his unquestioning acceptance of the hypothesis of electrical axis.⁵ That is the purpose of this report. We accept Wilson and associates' classification of human right and left bundle branch block⁶ rather than that of Lewis and his predecessors. The former is completely supported, at least as far as what is now called left bundle branch block is concerned, by the observations of Wolferth and Margolies⁷ on the time relationships of various right and left ventricular potentials in bundle branch block. For this reason and others that will be discussed later, it seems clear that although there is little reason to question the correctness of Lewis' ideas as to the side of the lesion in experimental canine bundle branch block, he was led into error in his considerations of human bundle branch block. An attempt will be made to analyze the contributions of the right and left ventricle to various electrocardiographic leads in the human being.

The term dextrocardiogram is used to refer (in whatever lead is under consideration) to that part of the pattern of differences of potential which is presumably derived from electrical activity in the right ventricle and the part of the septum activated via the right ventricle. The term levocardiogram is used to refer similarly to the left ventricle and the part of the septum activated via the left side. These definitions correspond in one sense to Lewis' terms, true dextrogram and true levogram. We wish to avoid the connotation that the dextrocardiogram and levocardiogram necessarily reflect rotation of a supposed electrical axis in the right and left ventricles. Their values in any lead must obviously depend upon the contribution of each of the ventricles to the mean potential variations of the two (or more) positions in contact with the electrodes used to make a lead, irrespective of the mechanisms involved in the development of the potential variations.

When bundle branch block develops it may be assumed that intraventricular conduction throughout the uninvolved or "normal" ventricle remains relatively undisturbed by the bundle branch block and that in the "abnormal" ventricle the excitatory process is delayed and its spread aberrant. Moreover, the order of excitation of part of the septum is also subject to change. With normal conduction it is probable, as Lewis⁸ believed, that activation of the septum proceeds from both sides more or less simultaneously. If, however, bundle branch block occurs, there is little reason to doubt that activation of the entire septum as well as that of the "abnormal" ventricle proceeds from the undisturbed side. When intraventricular conduction fluctuates between a presumably normal type and bundle branch block, the electrocardiographic changes that occur are presumably due to intermittent existence of the previously mentioned disturbance mechanism.

When intraventricular conduction is normal, the QRS complex may be regarded as reflecting the summation of right and left ventricular electromotive forces during that period (in other words, summation of the dextrocardiogram

and levocardiogram), although because of slight grades of asynchronism of activation, its beginning and ending may result from part of the activation of either one or the other ventricle alone. However, when bundle branch block develops, it may be assumed on the basis of experimental studies in dogs by Lewis⁵ that early deflections in the QRS complex in human beings (perhaps those recorded during the first 0.04 to 0.06 second) reflect the electrical activity which occurs during such a period in the "normal" ventricle, the septum, and, perhaps, some of the myocardium near the septum, ordinarily activated via the other ventricle, whereas the late deflections added to the QRS complex reflect aberrant spread of the excitatory process in the "abnormal" ventricle.

For these reasons, analysis of the similarities and differences in the deflections of ventricular complexes in patients who at one time exhibit normal intraventricular conduction and at another time bundle branch block should be a method of obtaining information regarding the contribution of one ventricle to electrocardiographic leads that does not have to depend on assumptions of uncertain value. At least one might hope to discover whether current views regarding the mechanism of bundle branch block can be reconciled with those of electrical axis and whether Lewis' ideas regarding the dextrocardiogram and levocardiogram have a useful application to human bundle branch block, even though he may have been in error as to the order of excitation. Accordingly we report here certain findings in the electrocardiograms of five patients who showed periods of alternation between presumably normal intraventricular conduction and right bundle branch block (Figs. 1 to 5); and for purposes of comparison, certain electrocardiographic leads of patients exhibiting transient left bundle branch block are included. In one (Fig. 6) the transition from left bundle branch block to normal type intraventricular conduction and back again to left bundle branch block, as recorded in Lead I, is shown. In the second (Fig. 7) the transition from left bundle branch block to normal intraventricular conduction in Lead III is shown. In the third, obtained from a patient with marked left ventricular enlargement (Fig. 8), a comparison of ventricular complexes obtained with an exploring electrode placed over the right side of the precordium during normal type intraventricular conduction and during left bundle branch block is illustrated. In the fourth (Fig. 9) two isolated beats that exhibit recovery from left bundle branch block are shown in a CR₁ lead.

Criteria for Selection of Cases Showing Right Bundle Branch Block.—In selecting the cases of right bundle branch block for this presentation an attempt was made to avoid the possibility that differences in ventricular complexes which developed in association with bundle branch block were due to any other ventricular change than the bundle branch block itself. This possibility is avoided in Case 1 (Fig. 1) because each lead shows both normal and bundle branch block types of complexes. It is likewise avoided in the limb leads of Case 2 (Fig. 2, B) for the same reason. Moreover, in Case 2 the electrocardiogram preceding the episode of bundle branch block (Fig. 2, A) was found to be essentially the same as one obtained after the disappearance of bundle branch block. In Cases 3 and 4 (Figs. 3 and 4, respectively) the transition between normal

type intraventricular conduction and right bundle branch block was not recorded, but in each instance the ventricular complexes obtained before and after the episodes of bundle branch block shown were essentially the same. The bundle branch block in Case 5 occurred during an attack of acute pericarditis. The QRS complexes before and after bundle branch block were essentially the same but there were changes in the T waves.

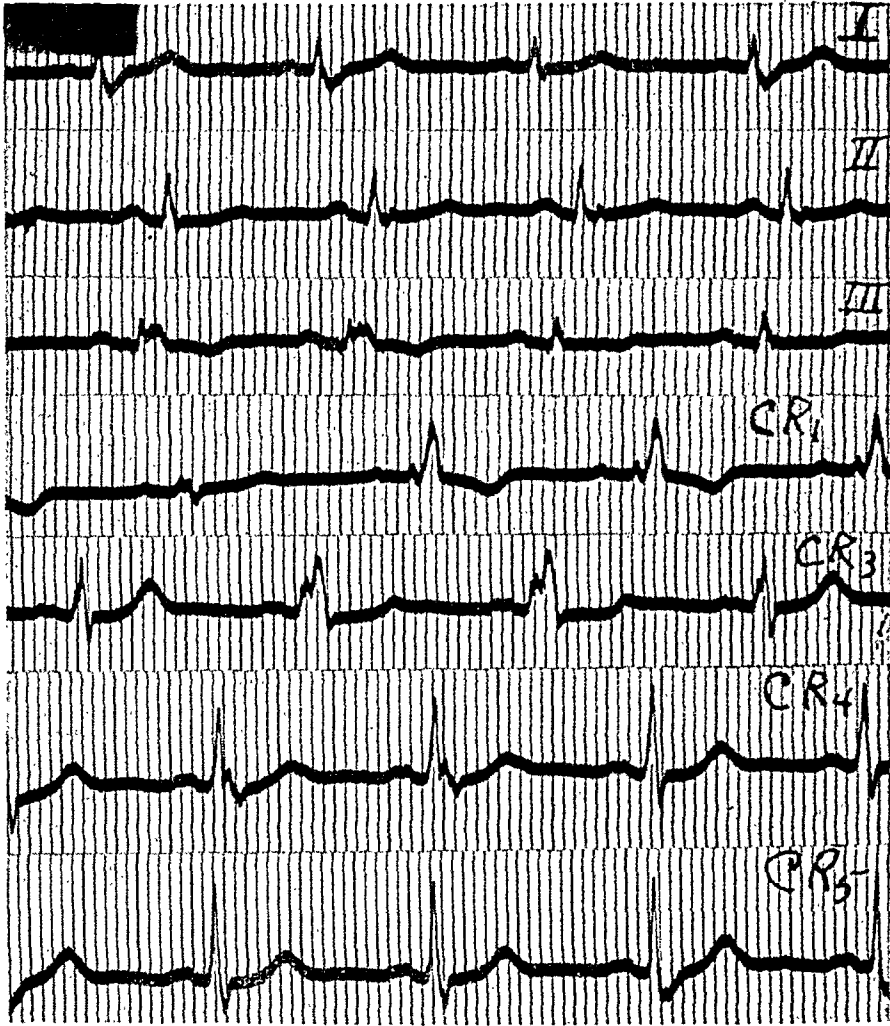


Fig. 1.—Case 1. Beats exhibiting normal type intraventricular conduction and right bundle branch block in all leads. In beats of the normal type the ascending limb of the intrinsic-like deflection in CR_3 is relatively late, being preceded by an upward deflection less steep in slope. The latter corresponds in time to the upward limb of the intrinsic-like deflection found in Leads CR_4 and CR_5 . The fact that even in Leads CR_1 and CR_3 the first 0.03 second of the QRS complex is not altered by right bundle branch block indicates that this part of the complex is left ventricular in origin in both types of beat. In limb leads and in Leads CR_4 and CR_5 , in contrast to CR_1 and CR_3 , the main deflections of the QRS complex and the T waves are found to change only slightly as a result of right bundle branch block.

Clinical Data in Cases of Right Bundle Branch Block.—None of the five patients was hypertensive, showed any signs of valvular disease, or was found to have enlargement of either ventricle by x-ray examination.

Case 1, a man 58 years of age, discovered in a so-called health survey, was working full time, regarded himself as healthy, and had no symptoms nor history of heart disease. Case 2, a physician 65 years of age, had been disabled for several years by the anginal syndrome. About a year after the episode of bundle branch block was recorded he began to exhibit electrocardiographic changes pointing to damage of the left ventricle. Case 3, a university professor 64 years of age, had previously suffered from A-V heart block and mild Adams-

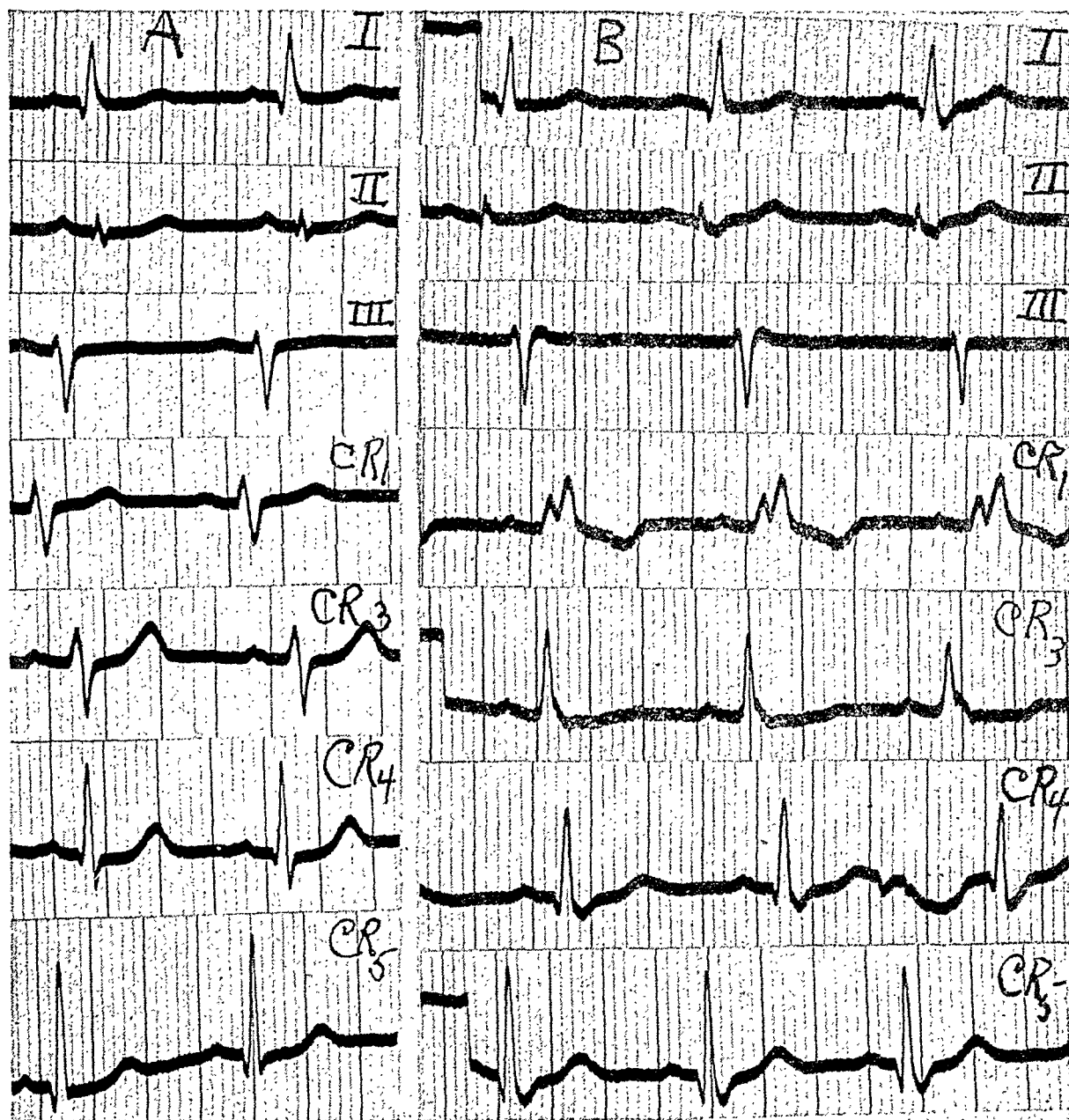


Fig. 2.—Case 2. A was obtained prior to the episode of transient intermittent right bundle branch block shown in B. In the latter, both normal type beats and right bundle branch block are found side by side in limb leads, although all beats in precordial leads are of the bundle branch block type. The disturbance of mechanism in this case is slightly different from that in Case 1 in that in Leads CR₁ and CR₃ differences in ventricular complexes of the two types of beats exist from the very beginning of the QRS complex. The ascending limbs of the first deflection of CR₁ look somewhat alike, but the slope is less steep in bundle branch block. As in Case 1, the main deflections of the QRS complex and the direction and amplitude of T waves in limb leads and precordial leads CR₄ and CR₅ are little influenced by bundle branch block.

Stokes seizures. Case 4, a business executive 59 years of age, had suffered an attack of acute coronary occlusion with posterior myocardial infarction several years prior to the occurrence of bundle branch block but had made a good recovery. Case 5 (Fig. 5), a woman 61 years of age, developed what appeared to be acute pericarditis following a surgical operation. During this period one electrocardiogram, made when the cardiac rate was quite rapid, showed right



Fig. 3.—Case 3. A was obtained prior to B, which exhibits right bundle branch block. Following the episode of bundle branch block, another electrocardiogram was obtained similar to A. As in Case 2, Leads CR₁ and CR₃ show changes in the QRS complex from its beginning. The main deflections of the QRS complex and T wave of limb leads are little changed by right bundle branch block. There are minor differences in the QRS complexes of Leads CR₄ and CR₅.

bundle branch block. This finding raised a rather pointed question as to whether the pericarditis might not be associated with myocardial infarction, a possibility that could not be ruled out completely. It seemed proper to include this case, however, because the QRS complexes obtained in tracings before and after the bundle branch block were essentially the same.

Changes in QRS Complexes Associated With Right Bundle Branch Block.—One of the most striking phenomena observed in the five cases of right bundle branch block was the lack of pronounced change in the main deflections of the QRS complexes in limb leads as a result of bundle branch block. In Cases 1,

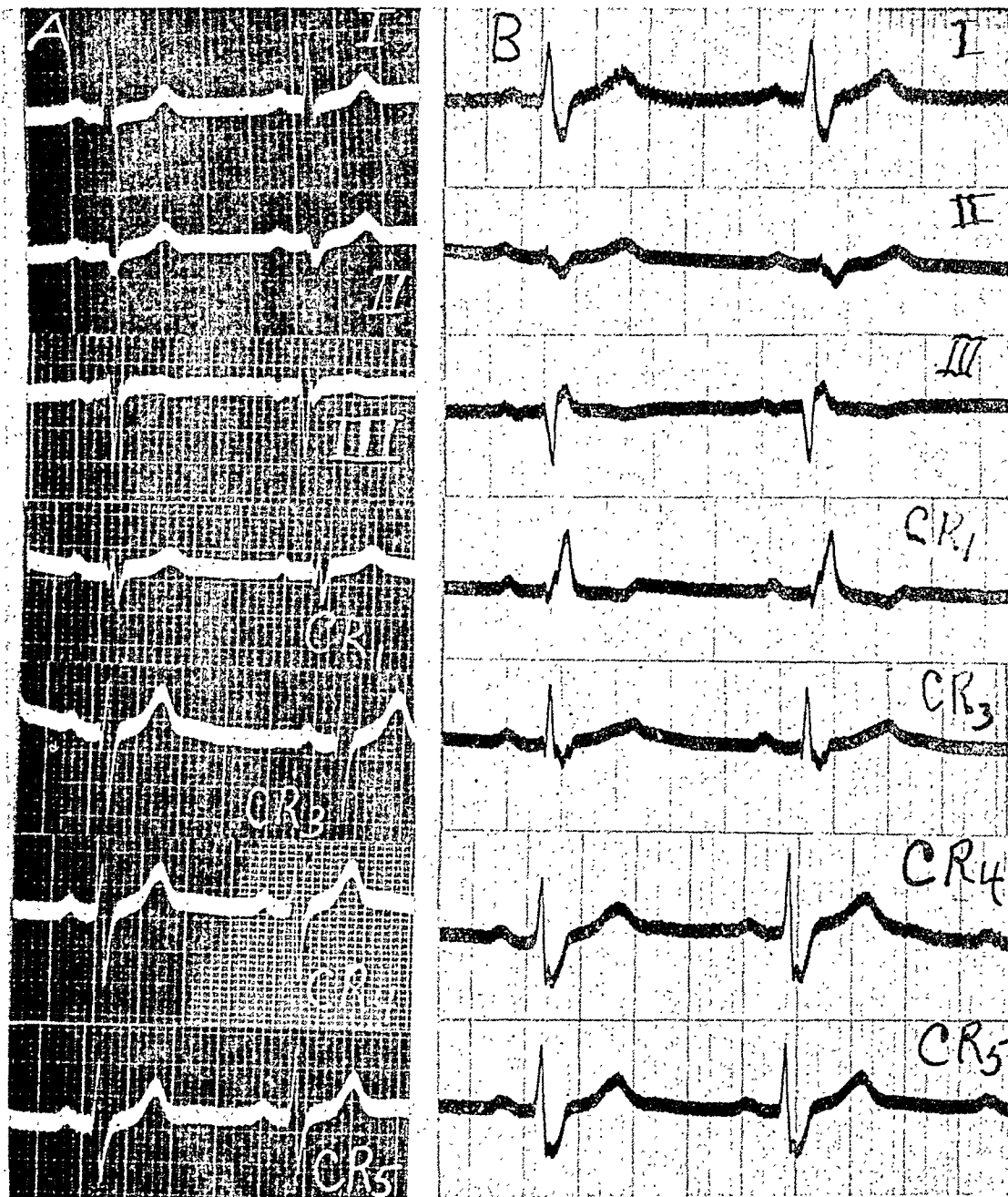


Fig. 4.—Case 4. A, made with a portable machine, was obtained prior to the episode of right bundle branch block shown in B. Allowance must be made for the differences in speed of photographic paper as well as the faster response of the beam of the machine used to obtain B. Very slight changes in the early part of the QRS complex in Leads II and III occur during bundle branch block. The T wave changes, although minor except in CR₁ and CR₃, are great enough to cause change of direction in Lead III.

2, and 3 the limb leads were practically identical during normal conduction and during periods of bundle branch block. In Case 4 (Fig. 4), a small upward deflection was observed early in the QRS complex in Lead II during bundle

branch block that was not recorded when the intraventricular conduction time was within normal limits. In Lead III, however, there was a correspondingly small initial upward deflection in the "normal" tracing which practically dis-

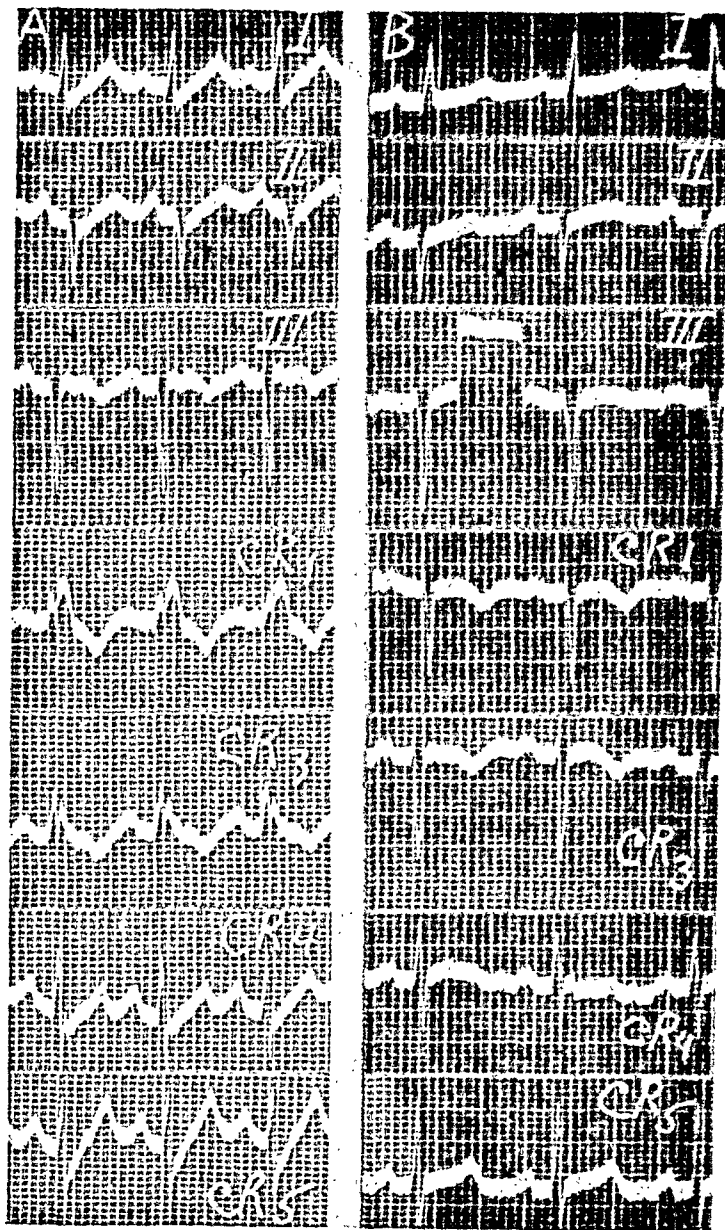


Fig. 5.—Case 5. A was made during a transient period of right bundle branch block and B, two days later. Although the main deflections of the QRS complex are much the same in limb leads and precordial Leads CR₄ and CR₅, there are slight differences in the initial part in limb leads. The differences are marked in CR₁ and CR₃. The T-wave changes may be attributed in part to the active pericarditis present when both tracings were made.

appeared during bundle branch block. In Case 5 (Fig. 5) there were also minor differences in the beginning of the QRS complex in association with bundle branch block. The most conspicuous difference was the loss of a very small initial

upward deflection in Lead II and the disappearance of slight slurring in the beginning part of the downward deflection in Lead III. In all cases the broad terminal deflection developed and prolonged the duration of the QRS to at least 0.12 second, as is characteristic of right bundle branch block. This deflection doubtless reflects the delayed aberrant excitation of the right ventricle.

In comparisons of patterns of precordial leads made at different times, one must allow for the possibility that the relationship of position of exploring electrode and cardiac surface may not be identical. In spite of this limitation, the findings in these five cases permit certain definite statements. Thus, in leads made with the exploring electrode placed on the right side of the precordium, such as in Lead CR₁, radical changes develop in association with bundle branch block. In some instances, however, the pattern of the QRS complex is not altered by bundle branch block during the first 0.02 to 0.03 second (Figs. 1 and 4). In others it differs from the very beginning (Fig. 5). In Lead CR₃ the similarity in the beginning of the QRS complexes exists in the same cases in which there is a similarity in CR₁. The main deflections of the QRS complexes recorded with the exploring electrode placed over the left side of the precordium, such as in Leads CR₄ and CR₅, showed remarkably little change as a result of right bundle branch block, although minor differences were observed in Cases 3, 4, and 5 (Figs. 3, 4, and 5).

In all cases the broad terminal deflection during right bundle branch block was relatively large, more or less rounded, and upwardly directed in leads made with the exploring electrode placed over the right side of the precordium. The deflection was much smaller and downwardly directed in leads made with the exploring electrode placed over the left side of the precordium.

Changes in the T Waves Associated With Right Bundle Branch Block.—In the comparison of T waves during normal type intraventricular conduction and right bundle branch block, Case 5 is excluded for reasons stated previously. In the other cases, changes in the amplitude of T waves in limb leads occurred but most of them were minor. Thus, in Lead I of Cases 1, 2, and 3, the T waves were slightly larger during bundle branch block, and in Case 4 they were about the same size. In Lead II changes were very slight. In Case 3 the T waves were definitely smaller in Lead III during bundle branch block, and in Case 4 they changed from practically isoelectric to slightly inverted. The most marked changes in T waves, as well as in QRS complexes, were noted in leads made with the exploring electrode placed over the right side of the precordium. Thus, in Cases 1, 2, 3, and 4 the T wave changed from upright to inverted when right bundle branch block occurred. In the CR₃ leads the T waves also showed marked changes. However, in CR₄ and CR₅ leads the T wave changes were slight and in no instance was the direction changed. In three cases the amplitude of the T waves was slightly smaller and in one case slightly larger in CR₄ leads during bundle branch block. However, in CR₅ leads the T wave was slightly smaller in one case and larger in three cases during right bundle branch block.

Changes in the Ventricular Complexes in Association With Left Bundle Branch Block.—It is obvious from inspection of Figs. 6, 7, and 8 that the patterns of

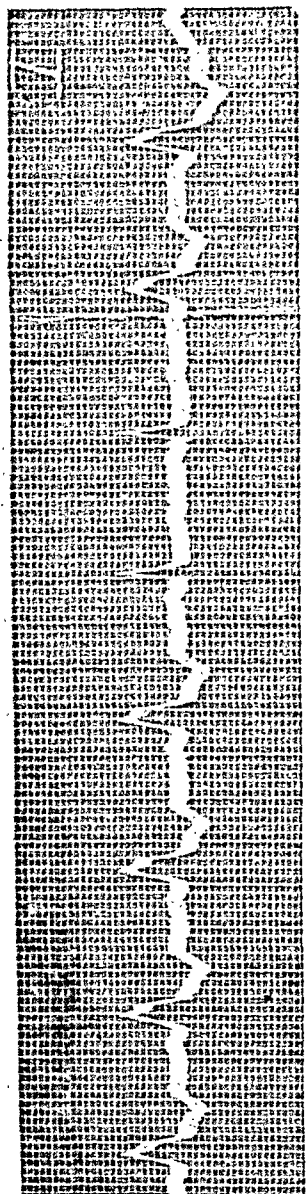


Fig. 6.—Interruption of left bundle branch block by two normal type beats in Lead I. No resemblance was noted between the ventricular complexes in the two types of beats.

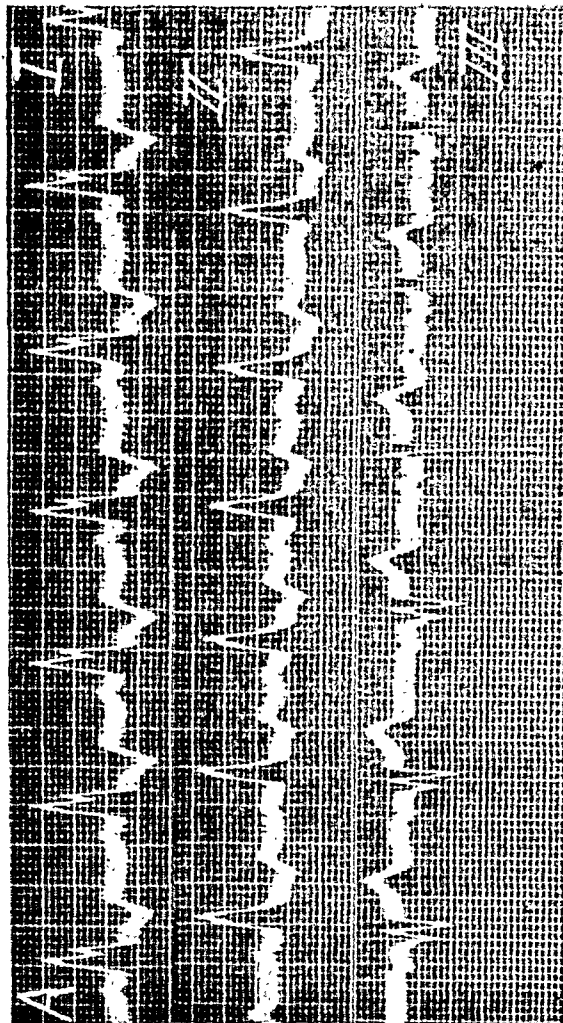
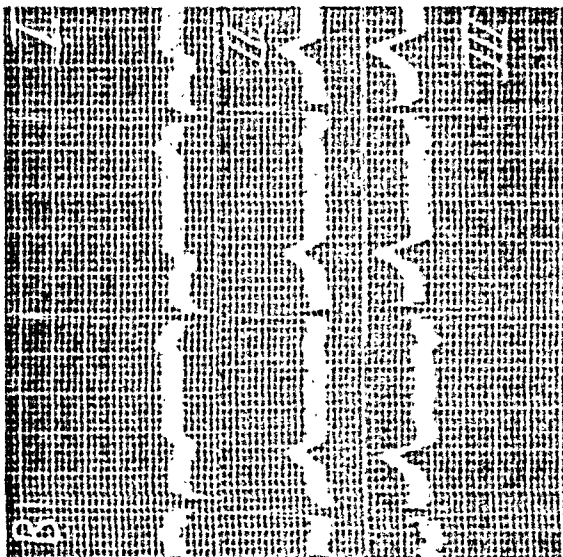


Fig. 7.—A shows change from left bundle branch block to beats with normal intraventricular conduction time in Lead III. B, obtained later, shows a marked grade of so-called left axis deviation. No resemblance was noted in the QRS complexes of the two types of beats in any of the three leads. The resemblance of T waves in Lead III is probably a coincidence. The differences in Lead II are quite marked.



ventricular complexes are radically changed in Leads I and III when left bundle branch block develops. Thus, the QRS complex in these leads shows no resemblance whatever to the pattern found during normal type intraventricular conduction.* In fact, the only resemblance of QRS complexes we have ever been able to discover is found in leads made with the exploring electrode placed over the right side of the precordium. In such leads there is always a sharp downwardly directed movement early in the QRS complex both during normal type intraventricular conduction and left bundle branch block. In both conditions this downward movement is usually, but not always, preceded by an upward movement so that a peak is formed above the isoelectric line. The upward movement tends to be smaller in bundle branch block (Figs. 8 and 9).

Usually there is marked change in the T wave with the development of left bundle branch block, as in Fig. 6. Fig. 7 is exceptional in that the T wave in Lead III shows little change following reversion to normal type intraventricular conduction. This was probably a coincidence because the T waves in Leads I and II were markedly changed by bundle branch block.

DISCUSSION

In the five cases of transient right bundle branch block presented, it is clear that, if current views regarding the aberrant course of the excitatory process in the two main types of bundle branch block are correct, the main deflections of the QRS complex in limb leads were contributed almost entirely by the left ventricle and the part of the septum activated via the left ventricle. The right ventricle and the part of the septum ordinarily activated by it appear to have had very little influence in the formation of these deflections. Moreover, the influence of the right ventricle on the characteristics of the T waves in limb leads also appears to have been slight. The "bicardiogram" or actual electrocardiogram in limb leads was formed almost entirely by the "levocardiogram." This statement applies equally to our cases with "left axis deviation" and "normal electrical axis." It should be emphasized that these were cases without evidence of right ventricular enlargement or hypertrophy. Had we been dealing with such cases, much greater changes in the main deflections of the QRS complex and, perhaps also the T waves, might have been expected as a result of right bundle branch block. One of Wilson's⁶ patients having mitral stenosis, showed more change than any of our patients.

The radical change in the entire ventricular complex in limb leads caused by left bundle branch block adds further support to the view that the left ventricle was the structure in that group of cases almost entirely responsible for the pattern found when intraventricular conduction was of the normal type. An objection to the thesis that the right ventricle contributed relatively little to limb leads in these cases may be raised on the ground that differences of potential of considerable magnitude developed early in the QRS complexes during left

*The statement has sometimes been made that there is a resemblance between limb lead ventricular patterns of certain cases with marked left ventricular enlargement and those of left bundle branch block. Examination of the actual deflections, however, shows that what similarity exists is merely a coincidence (Fig. 8).

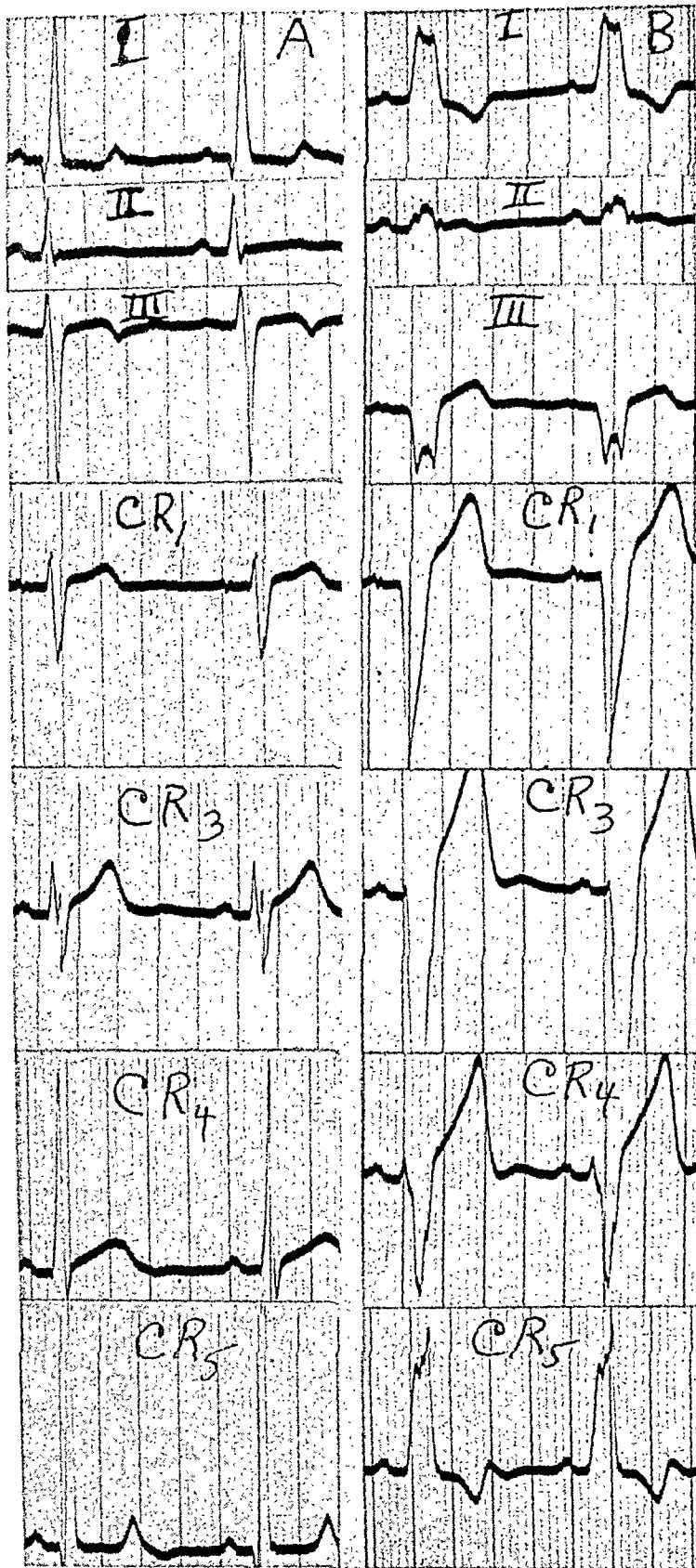


Fig. 8.—The patient from whom these electrocardiograms were obtained had rheumatic type of aortic insufficiency with great enlargement of the left ventricle. In the limb leads and the precordial leads CR_4 and CR_5 no resemblance between beats exhibiting the two types of intraventricular conduction could be observed. In the precordial leads CR_1 and CR_3 during bundle branch block a large early deflection of the QRS complex is noted which may represent the right ventricular component of the early deflection recorded in the QRS complex of CR_1 in A. The sharp downward deflection of the QRS complex, beginning 0.06 second after the beginning of the complex in Lead CR_4 , B, probably reflects excitation of the part of the surface of the left ventricle adjacent to the septum.

bundle branch block, presumably before activation of the left ventricle took place. The explanation for this must await more detailed studies of the course of the excitatory process in left bundle branch block. However, during the early part of the QRS complex the excitatory process, in addition to activating the

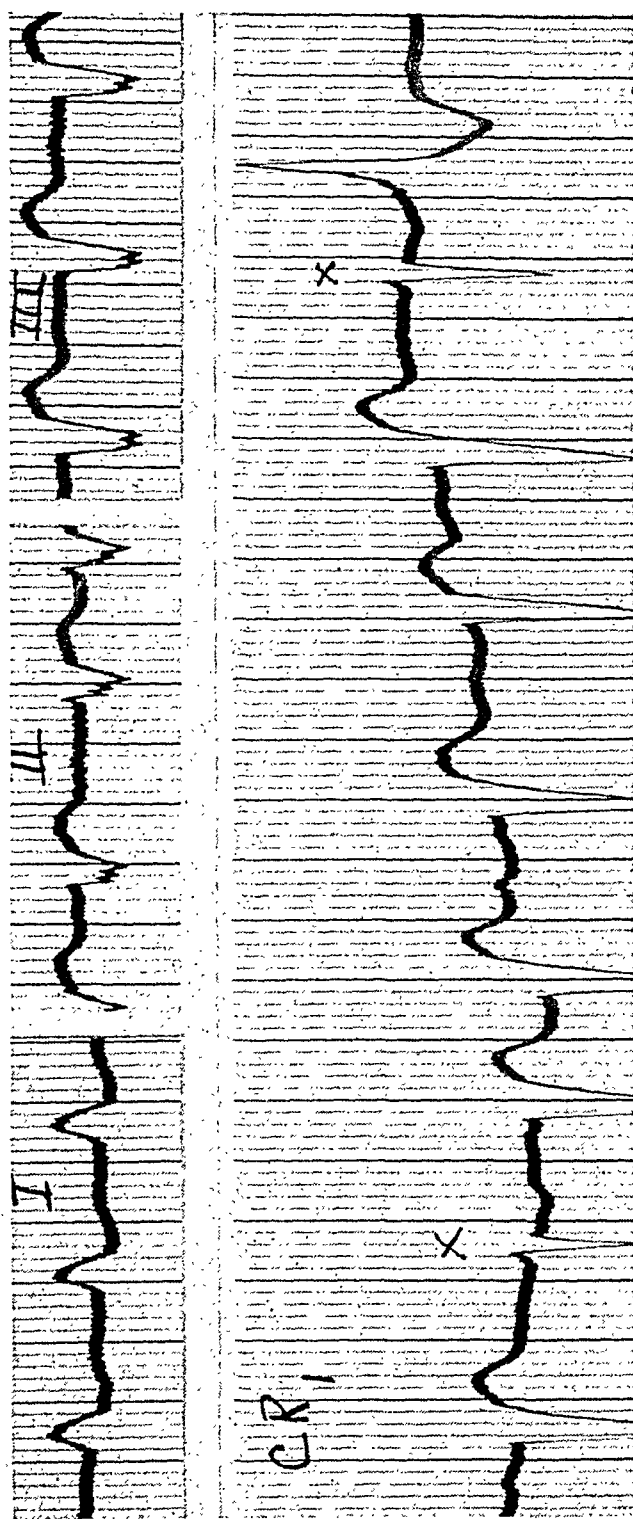


Fig. 9.—Auricular fibrillation and left bundle branch block. The second and eighth beats in the precordial lead CR₁ marked X show temporary recovery from left bundle branch block. Note the resemblances of an early deflection of the QRS complexes in both types of beats. The differences are that in the normal type beats it falls a little later, the upward limb seems slightly larger, and the descent is less in amplitude.

right ventricle, also must begin its aberrant course throughout the left side of the septum and it may also reach contiguous parts of the left ventricle.*

Lewis⁵ noted in experimental canine bundle branch block that direct leads made from the ventricular surfaces showed no delay in the arrival of the intrinsic deflection at the exterior surface of the contralateral ventricle, whereas in the case of the homolateral ventricle, the conduction tracts of which had been transected, the arrival of the intrinsic deflection was markedly delayed (up to 0.035 to 0.04 second). Wilson and co-workers⁶ found that the intrinsic-like deflections of semidirect leads exhibited the same behavior. He also observed that a precordial lead shows a marked resemblance to that of the underlying semidirect lead. Thus the chain of evidence in the dog demonstrating that the pattern of a precordial lead resembles the pattern of a lead made with an exploring electrode placed on the directly underlying surface of the ventricular myocardium was completed. However, among the qualitative differences in pattern between a precordial lead in bundle branch block and a direct lead from the underlying ventricular surface is the fact that in precordial leads made with the exploring electrode placed over the side of bundle branch block, the intrinsic-like deflection tends to be lost.† On the other hand, it is well preserved in precordial leads made with the exploring electrode placed over the side of the "normal" ventricle. The reasons for this difference need not be elaborated here beyond stating that the most important reason probably is that in the normal ventricle a comparatively large area of surface is excited at practically the same time with summation of electrical effects, whereas in bundle branch block excitation of an area the same size is a much longer drawn-out process, with less summation, somewhat similar to that of auricular excitation. In any event, it is the behavior of the right- and left-sided intrinsic-like deflections in precordial leads that furnishes the key to the recognition of the side of the lesion in bundle branch block or in even lesser grades of intraventricular conduction defect. If, however, the right-sided intrinsic-like deflection is a little late when intraventricular conduction is of the normal type, as in Case 4 (Fig. 4), the fraction of the QRS complex that precedes it does not necessarily change when bundle branch block develops.‡

*The sharp downward deflection, usually beginning about 0.04 to 0.06 second after the beginning of the QRS complex, which is recorded in almost all cases of left bundle branch block (but only in leads made with the exploring electrode placed on a localized area, usually a little toward the left side of the precordium), probably reflects the arrival of the excitatory process at a part of the anterior surface near the septum ordinarily activated via the left ventricle (Fig. 8, B, Lead CR₄).

†The terms right- and left-sided intrinsic-like deflection, as used in this paper in connection with precordial leads, refer to the combinations of sharp upward and downward movements, each forming a peak in the QRS complex of certain leads. The upward and downward movements are regarded as a unit irrespective of their relation to the base line. The left-sided intrinsic-like deflection, when it is not abolished or modified by disease or a conduction defect involving the anterior wall of the left ventricle, is easily recognized. The right-sided deflection, in which the upward and downward movements, especially the former, are usually much less in amplitude, may be obscured by "unexplained deflections" introduced via the reference electrode unless it is placed on the right arm or preferably over the spine of the right scapula.

‡Minor grades of intraventricular conduction defect constitute an almost unexplored field. There can be little doubt that duration of the QRS complex as the sole criterion is unsatisfactory even though the attempt is made to develop standards that take into account the size of ventricles. Thus, the right-sided intrinsic-like deflection, which probably signals the passage of the excitatory process through the anterior wall of the right ventricle, usually occurs very early in the QRS complex. However, it can be subject to pronounced delay without actual prolongation of the QRS complex (Fig. 1, Lead CR₃; and unpublished observations). The part of the QRS complex that precedes it is not necessarily derived

In other words, under these circumstances the initial part of the QRS complex may be levocardiogram when intraventricular conduction time is within normal limits. If it is, the development of right bundle branch block extends the period of the unmodified levocardiogram in the electrocardiogram until the delayed aberrant excitatory process begins to activate the right ventricle. The influence of the right ventricle on the QRS complex of precordial leads made from the left side of the precordium as well as limb leads, however, is so negligible that even when the right-sided intrinsic-like deflection occurred at the very beginning of the QRS complex, its disappearance, as a result of bundle branch block, caused, at most, insignificant changes in the early part of the QRS complex of those leads. Thus, in these cases, it was only in leads made with an exploring electrode placed over parts of the precordium near the right ventricle that this structure exerted an important effect on the form of the main deflections of the QRS complex.

The almost constant finding of inverted T waves in CR leads made from the right side of the precordium in right bundle branch block can be attributed, at least in part, to the aberrant course of the excitatory process in the right ventricle and consequent aberrant order of return to the resting phase. The evidence for this is that in each of our cases inversion of the T wave developed only when bundle branch block was present. Moreover, it seemed equally clear that right ventricular electrical activity had only slight influence on the T waves in CR leads recorded from the left side of the precordium, because they were only slightly changed as a result of right bundle branch block, despite the pronounced changes in the T waves in leads made with an exploring electrode placed over the right side of the precordium.

The direction and relative amplitude of the broad terminal deflection of the QRS complex in right bundle branch block in the various precordial leads appear to show the same type of behavior in all cases. First of all, its characteristics indicate that even though normal type excitation of the right ventricle may have little effect on the QRS complex and T wave of certain leads, an abnormal delayed type of excitation can be registered distinctly at the end of the QRS complex of the same leads. This abnormal deflection, like RS-T segment displacement following obstruction of a coronary artery, presumably arises from abnormal electrical activity in a limited part of the heart (in right bundle branch block, the right ventricle) and occurs, at least in part, during a period of time when it is not obscured by deflections caused by activity elsewhere in the heart. Although the mechanisms responsible for these two types of deflections are totally different, their behavior is in some respects analogous. Thus, in both the displacement is upward when the exploring electrode is placed directly over the area of involvement, and it is greater in such leads than in any other. Moreover, in both conditions, when the exploring electrode is placed at a distance

entirely from the left ventricle but might be derived in part from excitation of some other part of the right ventricle. Under such circumstances, if right bundle branch block developed, the initial part of the QRS complex as well as the intrinsic-like deflection would be modified or would disappear from leads made from the right side of the precordium, depending on the time relations of the right-sided intrinsic-like deflection, the beginning of excitation elsewhere in the right ventricle, and the beginning of excitation of the left ventricle prior to the development of bundle branch block.

from the area of involvement, the displacement is in the opposite direction and the amplitude is less. Thus, it would appear that the principle governing reciprocal relationships of direction of RS-T segment displacement at various parts of cardiac surfaces,⁹ which is reflected in body surface leads, also applies, to some extent at least, to the broad terminal deflection of right bundle branch block. It is probable that the opposite directions of the deflection in the terminal portion of the QRS complex in left bundle branch block in leads made from the right and left sides of the precordium furnish a manifestation of the same principle regarding the distribution of potential.

In view of the foregoing findings, the possibility that Wilson's views regarding the classification of bundle branch block are incorrect and that what is now called right bundle branch block is actually left bundle branch block and vice versa should be reconsidered. On the basis of the evidence presented here the proponents of this view would have to maintain that when intraventricular conduction is of the normal type the right ventricle is almost entirely responsible for the pattern of ventricular complexes in limb leads and that the left ventricle, despite the fact that its muscle mass is usually far greater than that of the right ventricle, exerts a negligible influence. Greater trouble would arise in trying to account for the findings in precordial leads. It would be necessary to assume, in view of the positions of the exploring electrode at which the greatest changes occur in bundle branch block, that activation of the left ventricle produces far greater potential variation over the right side of the precordium than over the left, which is much nearer to it, and that the right ventricle produces far greater potential variation over the left side of the precordium than over the right side. Such an assumption would have to ignore the findings in Wilson's studies of semi-direct and precordial leads in experimentally produced canine bundle branch block,⁶ which indicate that patterns of differences of potential recorded with an exploring electrode on a precordial surface tend to resemble those obtained with the electrode close to the directly underlying part of the ventricular muscle. As a result of such observations, as well as those of Wolferth and Margolies referred to earlier, it has seemed to us that Wilson's views regarding the electrocardiographic criteria that reveal the side of the lesion in bundle branch block are sound. The doubt that has been expressed in the past has been on the basis of limb lead criteria which are admittedly not completely satisfactory in some cases. There has been no effective criticism of the validity of the evidence derived from cardiac surface and precordial leads.

Inasmuch as the changes in electrocardiograms that develop as a result of bundle branch block are not in accord with the hypothesis of electrical axis, irrespective of whether current views regarding bundle branch block are satisfactorily established, the fault must be with the hypothesis of electrical axis. What evidence there is to favor that hypothesis has been fully presented many times and does not require repetition here. It should be said, however, that the evidence to support it, which is obtained from changes in electrocardiograms that result from change in position of the heart or enlargement of one or the other ventricle, begs the question because the hypothesis was constructed to account for such findings. The fact that Lewis, reasoning accurately, could use it to his

complete satisfaction to account for the deflections of QRS complexes in human bundle branch block, even though he was mistaken as to the side of the lesion, illustrates the nature of what can happen if this pitfall of logic is not avoided.

The results of the present study considered alone do not rule out application of the concept of electrical axis to electrocardiograms, although they necessitate certain modifications of present ideas. One may still assume, if he wishes, that an axis rotates. He is forced by the evidence to concede that rotation in the right ventricle, provided that chamber is not enlarged, exerts little influence on the patterns of the main deflections of the QRS complexes in limb leads. If, then, he assumes that the QRS complexes of limb leads are formed mainly by rotation of the axis in the left ventricle, he still has before himself the problems of explaining (1) the nature of the coincidence accounting for the fact that a pattern of differences of potential, recorded by the method of balanced potentials with an exploring electrode placed near the left border of the precordium, can be preserved, even including the intrinsic-like deflection, when the exploring electrode is moved to the left arm and (2) why (a) infarction in one part of the left ventricle causes change in rotation of the axis in one direction, (b) infarction in a second position causes change in rotation in the opposite direction, and (c) infarction in a third position causes no change in rotation. For such reasons we retain an interest only in the historic aspects of the hypothesis of electrical axis. It seems to be one of the numerous dubious results of attempting to apply to the body the laws that account for electrical behavior in models. It has not as yet been established that a complex aggregate of biologic structures like that of the human body behaves electrically like the physicist's models and there is some evidence against that view.¹⁰⁻¹²

The observations made here on bundle branch block support the concept that electrocardiographic leads can be analyzed from the point of view of summation of right and left ventricular effects (in other words, dextrocardiogram and levocardiogram) if one chooses to use those terms. However, the views of Lewis, based on reasoning that assumed the validity of the Einthoven equilateral triangle hypothesis, are not supported. The evidence is more in accord with the view that there are favored avenues of conduction between the heart and the extremities.¹² As far as precordial leads are concerned, the dextrocardiogram seems to play an important but not exclusive role in shaping leads made with an exploring electrode placed over the right side of the precordium, whereas the levocardiogram is predominant in leads made with an exploring electrode placed over the left side of the precordium.

SUMMARY

1. Five cases of transient right bundle branch block are reported which showed that the main deflections of the QRS complex in limb leads were very slightly altered as a result of right bundle branch block, although all cases showed the broad terminal deflection characteristic of that condition. The T waves of limb leads likewise showed only slight alterations during bundle branch block. Precordial leads made with the exploring electrode placed over the right side

of the precordium showed marked changes in both QRS complexes and T waves during bundle branch block. In some cases, however, there was no change in the earliest part of the QRS complex. Leads made with the exploring electrode placed over the left side of the precordium showed little change except for the broad terminal deflection of the QRS complex.

2. The development of left bundle branch block produced radical changes in the ventricular complexes of the same leads that were little changed by right bundle branch block. However, in the leads most radically changed by right bundle branch block (namely, those made with an exploring electrode placed over the right side of the precordium) an early deflection in the QRS complex was preserved, although somewhat modified in certain of its characteristics.

3. The changes in the ventricular complex that occur in bundle branch block indicate, provided current views as to the mechanism of bundle branch block are sound and also provided the right ventricle is not enlarged, that (1) the left ventricle and the part of the septum normally activated via the left ventricle are the source of electrical activity mainly responsible for the main deflections of the QRS complexes and also the T waves of limb leads, as well as leads made with the exploring electrode placed over the left side of the precordium when intraventricular conduction is of the normal type, and (2) the right ventricle is mainly, although not completely, responsible for differences of potential in leads made with the exploring electrode placed over the right side of the precordium. These findings are not in accord with views widely held regarding the parts played by the two ventricles in the hypothesis of electrical axis. They indicate that, except in leads made with an electrode placed near the right ventricle, the levocardiogram tends to contribute far more to the electrocardiogram than the dextrocardiogram. This, considered in connection with evidence that (1) certain parts of the left ventricle are electrocardiographically silent as far as "axis" is concerned and (2) by certain methods of pairing electrodes the pattern of differences of potential obtained with an exploring electrode placed just to the left of the precordium closely resembles that obtained by moving the exploring electrode to the left arm, appears to expose the hypothesis of electrical axis to the charge of having been a hindrance to progress in understanding the nature of the mechanisms concerned in the formation of electrocardiograms.

REFERENCES

1. Wolferth, C. C., Livezey, M. M., and Wood, F. C.: The Relationships of Lead I, Chest Leads From the C₃, C₄, and C₅ Positions and Certain Leads Made From Each Shoulder Region: The Bearing of These Observations Upon the Einthoven Triangle Hypothesis and Upon the Formation of Lead I, *AM. HEART J.* 21: 215, 1941.
2. Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, *Am. J. M. Sc.* 203: 641, 1942.
3. Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Distribution of the Patterns of Ventricular Potential Which Determine the Forms and Significance of Electrocardiograms, *Am. J. M. Sc.* 205: 469, 1943.
4. Wolferth, C. C., and Livezey, M. M.: A Study of Methods of Making So-Called Unipolar Electrocardiograms, *AM. HEART J.* 27: 764, 1944.
5. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, *Phil. Tr. Roy. Soc. London s.B.* 207: 221, 1916.

6. Wilson, F. N., MacLeod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, *AM. HEART J.* 7: 305, 1932.
7. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle Branch Block, *AM. HEART J.* 10: 425, 1935.
8. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons, Ltd., p. 104.
9. Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationships to Positive Displacement; an Experimental Study, *AM. HEART J.* 29: 220, 1945.
10. Gildemeister, M.: Ueber elektrischen Widerstand, Kapazität und Polarisation der Haut, *Arch. f. d. ges. Physiol.* 176: 84, 1919.
11. Eyster, J. A. E., Märesh, F., and Krasno, M. R.: The Nature of the Electrical Field Around the Heart, *Am. J. Physiol.* 106: 574, 1933.
12. Katz, L. N.: Concerning a New Concept of the Genesis of the Electrocardiogram, *AM. HEART J.* 13: 17, 1937.

TOBACCO ANGINA

AN ELECTROCARDIOGRAPHIC STUDY

J. MARION BRYANT, M.D.,* ANN ARBOR, MICH., AND J. EDWIN
WOOD, JR., CHARLOTTESVILLE, VA.

SINCE Huchard used the term tobacco angina in 1899,¹ there has been much discussion of the relation which it suggests, but few definitive studies of this relation have been published. A review of the literature reveals only two case reports which present objective evidence of myocardial ischemia during anginal seizures induced by smoking.² It is the purpose of this paper to discuss some of the cardiovascular effects of tobacco and some observations in sixteen patients with angina pectoris in whom electrocardiograms were taken immediately after the patient had smoked two cigarettes.

Numerous observers have expressed the opinion that a close temporal relation between the use of tobacco and the onset of cardiac pain is exceedingly rare.³⁻⁵ The majority of articles dealing with tobacco angina present little or no evidence that smoking is a cause of anginal seizures.^{1,5-12}

Investigation of the effects of tobacco in man have been concerned mainly with the response of the peripheral vascular system. It is generally agreed that smoking usually induces arteriolar constriction, accompanied by lowering of the temperature of the skin and elevation of the blood pressure, pulse rate,¹³⁻²¹ and blood sugar.²² There are, however, various opinions with respect to the particular products of smoking responsible for these phenomena and the mechanisms through which they are effected. The question of an allergic response to tobacco smoke in certain cardiovascular diseases has been raised, but the evidence bearing upon it is inconclusive.^{15,16,23-25}

There are many observations indicating that nicotine alone is capable of producing many of the reactions caused by smoking,^{16,19,20,26-28} but some investigators believe that the same cardiovascular responses are induced by smoking material that does not contain this drug.²⁰ The initial effect of nicotine is to stimulate, but its subsequent and more prolonged action is to depress the parasympathetic and sympathetic ganglia, central nervous system cells, and skeletal

From the Department of Internal Medicine, University of Virginia Medical School, Charlottesville, Va., and the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

Some of the observations reported in this article were made with the aid of grants from the Horace H. Rackham School of Graduate Studies, University of Michigan, and the Kresge Foundation.

Received for publication Oct. 7, 1946.

*Formerly Fellow in Cardiovascular Diseases, Department of Internal Medicine, University of Virginia Medical School, Charlottesville, Va.

muscles. The results which follow its administration are, therefore, complex and unpredictable; they represent a varying combination of many different effects.²⁸ The magnitude of the response to nicotine varies from one time to another.^{15,19} Studies of the effects of this drug and of tobacco smoke on the coronary blood flow have yielded conflicting results.²⁹⁻³¹ The complex action of nicotine and the many extrinsic as well as intrinsic factors influencing coronary flow suggests that this approach to the problem of its effects in man is of little value. Furthermore, as has been pointed out,² it cannot be assumed that diseased and normal coronary arteries will invariably react in the same way to a given stimulus. Physiologic and anatomic abnormalities are, so it would seem, likely to be found in company.

Statistical studies indicate that coronary disease develops before the seventh decade of life significantly more often in smokers than in nonsmokers^{32,33} and that the life span of the former is shorter.³⁴ Pathologic studies comparing the coronary arteries of these two groups have not been reported. Experiments on animals have brought forth no evidence that tobacco smoke or nicotine produces structural changes in these arteries.³⁵ After coronary ligation in dogs, there is a pronounced increase in the sensitivity to tobacco smoke and nicotine, as evidenced by cardiac arrhythmias.³⁶ It has not been proved that smoking has an effect on the coronary vessels comparable to its unquestioned deleterious effect on the peripheral arteries in certain diseases.^{37,38}

The most consistent effect of tobacco smoking upon the electrocardiogram of normal subjects is an acceleration of the heart rate with accompanying physiologic changes in the T wave,^{19,20,39-42} which involve a reduction in the size; less often, inversion of this deflection. Although it is known that in some persons smoking may raise the pulse rate without altering the blood pressure or cardiac output,⁴³ these electrocardiographic changes have usually been attributed to increased cardiac work.^{19,40,41} These changes have been referred to in a manner which suggests the inference that they are due to a direct effect of smoking upon the myocardium.^{4,28,41} However, it has been clearly demonstrated in the case of normal subjects and in the case of the majority of patients with heart disease that the changes in the T wave induced by smoking and those induced by other agents which elevate the resting heart rate to a similar level are alike in kind and magnitude.^{44,45} These electrocardiographic phenomena represent a physiologic response which has been studied both from the theoretical and from the empirical standpoint.^{45,46} The administration of drugs that slow the heart is accompanied by an increase in the height of the T wave and the administration of those drugs that accelerate the rate is accompanied by a decrease in the height of the T waves. The latter effect occurs even when the drug given belongs to the parasympathomimetic group.^{44,47}

There is a sharp difference of opinion concerning the mechanism through which smoking precipitates paroxysms of angina pectoris. One group of observers^{3,5,6,41,48} attributes all such paroxysms to increased cardiac work resulting from an elevation of the blood pressure and the heart rate and ignores or discounts the possibility of coronary constriction. Others^{1,2} believe that in some instances the occurrence of coronary spasm can hardly be doubted. Moreover,

from the time of Allbutt⁶ to the present time⁴⁹ the idea has persisted that there is a fundamental difference in the pathologic background between tobacco angina and true angina pectoris.

The most recent paper on the relation of smoking to angina pectoris is that of Pickering and Sanderson.⁵ In a detailed study of one patient, they found that smoking was attended by the occurrence of anginal pain only under certain circumstances; that is, only when the subject smoked immediately following the subsidence of a paroxysm precipitated by exercise and while a significant elevation of the pulse rate and blood pressure were still present. From these data, which did not include electrocardiographic tracings, the writers concluded that their "paper . . . has rendered redundant the hypothesis that constriction of the coronary arteries by tobacco is the cause of anginal attacks precipitated by smoking." This conclusion does not harmonize with numerous reports since the time of Heberden⁵⁰ to the effect that seizures were witnessed in which "the pulse was not quickened"⁵⁰⁻⁵² or in which no significant alteration in pulse or blood pressure occurred.^{2,53,54}

In 1939, Wilson and Johnston² studied two patients with angina pectoris in whom paroxysms and transient electrocardiographic changes, similar in magnitude and in kind to those produced by myocardial infarction, were induced by having the patients smoke. In one of these (Case 5) no alteration in the pulse rate or blood pressure accompanied the electrocardiographic changes. These observers suggested that, in certain instances, changes in the caliber of the coronary arteries or arterioles rather than increased cardiac work must be assumed to explain the attendant myocardial ischemia. Levy and collaborators⁵⁵ and Master and co-workers⁵⁶ have shown that, in patients with coronary insufficiency, painless myocardial ischemia induced by anoxemia or exercise can be demonstrated electrocardiographically. It is, therefore, possible that if Pickering and Sanderson had made electrocardiographic observations while their patient was smoking, they might have found evidence of myocardial ischemia without pain.

There is considerable evidence indicating that the coronary circulation is regulated by direct vasomotor control as well as by purely mechanical factors.⁵⁷⁻⁵⁹ It is the opinion of most investigators who have carried out experimental studies of coronary flow in animals that it is diminished by vagal and increased by sympathetic stimulation. The observations of Manning, Hall, and Banting,⁶⁰ that vagal stimulation in the intact dog uniformly produces areas of myocardial necrosis, which are most extensive after the prior administration of physostigmine and do not occur when atropine has been given, suggests that coronary spasm may be important in the production of myocardial ischemia. These experiments support the clinical observations of Gilbert,⁶¹ who found that in some cases of angina pectoris the administration of atropine definitely increases the coronary reserve as estimated by the Levy anoxemia procedure. The possibility that smoking may cause coronary constriction by stimulation of the vagi is suggested by Hobbs (quoted by Gilbert),⁶¹ who, in two patients with tobacco angina, demonstrated that atropine given prior to smoking prevented the occurrence of electrocardiographic changes of the type described by Wilson and Johnston.²

Moreover, Leary's suggestion,⁶² that coronary spasm in the absence of obvious coronary disease may sometimes be responsible for sudden death, emphasizes the importance of more adequate knowledge concerning reflex constriction of the arteries of the heart and the effect of tobacco upon this reaction.

MATERIAL

This report is based on observations in sixteen patients with coronary disease in whom the effect of smoking upon the electrocardiogram was investigated. In no instance did the clinical history indicate a relation between the use of tobacco and anginal symptoms. All of the patients had smoked for a long time, but the majority should probably be considered moderate rather than heavy smokers; some did not "inhale." The series includes substantially all patients with symptoms of the kind indicated who were seen in the electrocardiographic laboratory of the University of Virginia Hospital between September, 1943, and October, 1944, and who presented themselves during a period when time to carry out the required special tests was available. This group is composed of two women and fourteen men ranging in age from 38 to 69 years. The diagnosis of coronary disease was made on the basis of one or more of the following criteria: a history typical of angina pectoris; abnormal electrocardiographic findings at rest; or abnormal electrocardiographic changes precipitated by exercise (Master "two-step"), and anoxemia (Levy), or smoking. In two instances a diagnosis of recent anterior myocardial infarction was made on the basis of diagnostic changes in the precordial electrocardiogram.

METHOD

The tests were performed under uniform conditions. After the patient had rested in the recumbent posture for a time sufficient to give a basal heart rate, a control electrocardiogram consisting of the standard and unipolar limb leads was taken. Immediately thereafter the patient smoked two cigarettes of the brand to which he was accustomed. A second electrocardiogram was taken about ten minutes later when he had finished smoking or sooner if he experienced discomfort in the chest. This test was always carried out at least two hours after the last meal. None of the subjects were under the influence of any medicine which affects the cardiovascular system.

RESULTS

The most frequent response to smoking was an increase in heart rate averaging 10 beats per minute. The maximum increase was 28 beats per minute. In three instances no appreciable change in heart rate occurred. Gross changes in the RS-T segment were recorded twice. These will be discussed in detail later. The amplitude of the T waves in the remaining fourteen patients were measured from the T-P isoelectric level and were corrected for errors in the standardization of the electrocardiograph. A decrease in amplitude of 1 mm. or more in one of the standard leads was present in six instances; the maximum decrease was 2.0

mm. in Lead III and was associated with inversion of a previously upright deflection. In five patients the decrease in amplitude was less than 1 mm. while in three there was an increase in the height of T of less than 1 millimeter. Although these changes were small, their magnitude was directly proportional to the increase in heart rate. This relation has been noted previously.^{20,63}

Two 38-year-old men, who presented no objective evidence of cardiovascular disease but complained of precordial pain on exertion, exhibited T-wave changes after smoking similar in character but of lesser degree than those resulting from exercise in one case, and from exercise or anoxemia in the second case. These two cases have been reported in detail in a previous paper.⁶⁴

A number of the fourteen patients who presented T-wave changes associated with an increase in heart rate complained of tingling and coldness of the fingers and toes, sweatiness, nausea, and "dullness in the chest" not typical of angina pectoris.

CASE 1.—A practicing physician first came to the hospital in April, 1929. A diagnosis of psoriasis was made. At that time the blood cholesterol was 178 mg. per cent and the blood Wassermann was negative.

His next visit was in March, 1936, when he was 60 years of age. He then complained of a burning epigastric sensation which occurred when the stomach was empty and which was relieved by alkalis and food; there were frequent episodes of water brash and "heart burn" and occasional bouts of vomiting without hematemesis. There had been no melena. These symptoms had persisted for two or three years. In the two weeks prior to this admission the patient had had an acute febrile illness during which he had been conscious of irregularity of the heart and a mild orthopnea. Physical examination revealed an initial blood pressure of 172/100 which fell to 140/80 on bed rest. The size, rate, rhythm, and sounds of the heart were normal; no murmurs were present. The tonsils were inflamed. Psoriatic changes were present over the elbows. Examinations of the blood, urine, and stool were negative. Gastric analysis showed 7 degrees free and 20 degrees total acid but no other abnormality. Roentgenographic examination of the chest and upper and lower gastrointestinal tract revealed no abnormalities. An electrocardiogram consisting of the three classical limb leads was within normal limits.

On May 24, 1944, this man was seen for the third time. He described his condition as follows: "I can't say just when the pain started but would say it was sometime since the first of the year. I never noticed it before that time and when it first started I tried to attribute it to hyperacidity from which I suffered a great deal. But it was high up under the sternum, in my jaws, and occasionally out in the deltoid muscles. I began to suspicion it was angina since it would come on and leave in a short while, not lasting long. The pain was never very bad so that I would probably take something for it; and it would usually be relieved by sitting down, bending forward, and pressing against the sternum with my hands. It seemed that exertion had very little to do with it, and I was frequently in the habit of going over to my orchard (which is a steep mountain orchard) and walking for an hour or two without precipitating an attack." This discomfort occurred as often as twenty or forty times a day and could not be correlated with any particular activity or habit. He used two packages of cigarettes per day.

The physical findings at this time were essentially the same as those recorded eight years previously. A moderate degree of peripheral arteriosclerosis was present. Over the course of a hour the blood pressure varied from 220/95 to 180/85. The blood Wassermann and Kahn tests were negative. Laboratory studies revealed no abnormalities. Orthodiagraphic cardiac measurements (Kurtz) showed the heart to be of normal size, and fluoroscopic examination demonstrated no abnormality of the heart contour or lung fields. The thoracic aorta was dilated to a moderate degree.

An electrocardiographic study consisting of the standard and unipolar limb leads and multiple unipolar chest leads from a series of points extending from the right border of the precordium

around the left chest to the scapular line showed no definite abnormalities (see Fig. 1). A few minutes afterward, while the electrocardiographic film was being developed and inspected, the patient began to smoke a cigarette. After only a few puffs he remarked that a squeezing sub-sternal pain, an aching at the angle of both jaws, and a choking sensation had developed. A second electrocardiograph was immediately taken. However, the discomfort lasted only two or three minutes and disappeared before all leads were recorded. This tracing showed that, although

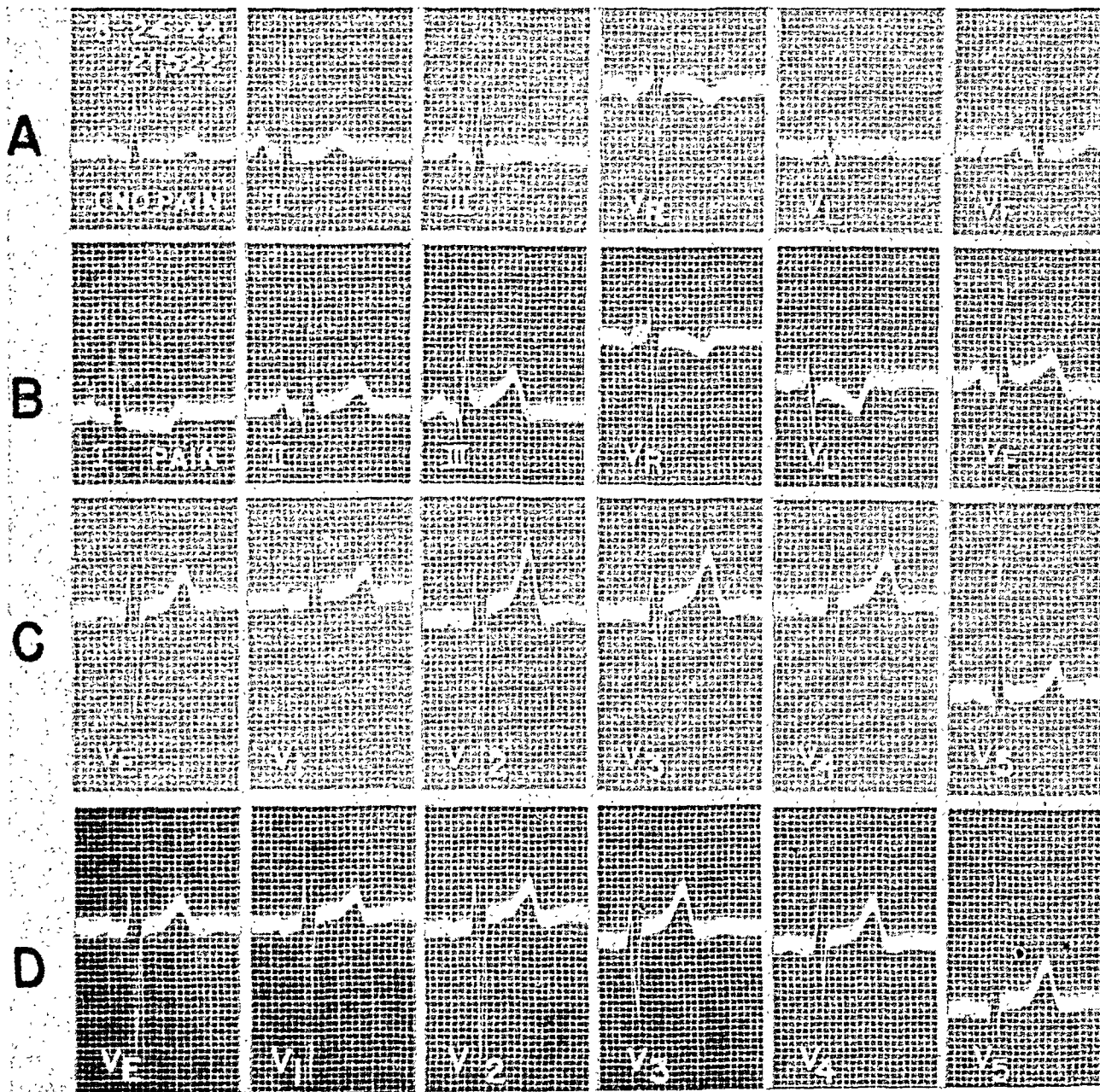


Fig. 1.—Case 1. Electrocardiograms taken before and during anginal seizure precipitated by smoking a cigarette. A, Limb leads before and, B, during smoking. C, Unipolar chest leads before and D, during smoking. Leads V_6 , V_7 , and V_8 are not shown.

the heart rate had not changed from the control speed of 57 beats per minute, pronounced RS-T depression in Lead I and RS-T elevation in Leads II and III had appeared. The unipolar limb and chest leads, however, showed no RS-T displacement, although they were obtained as quickly as the recording of from eight to twelve beats per lead permitted. While still recumbent, the patient then smoked another cigarette. After he had inhaled only two puffs, the discomfort

returned. He was asked to continue smoking, in spite of the pain, while another complete set of limb and chest leads was obtained. The discomfort continued while he smoked and disappeared within a few minutes after finishing the second cigarette. The discomfort was "not severe." No blood pressure determinations were made during the paroxysm.

The electrocardiograms obtained during the second episode of discomfort are reproduced in Fig. 1. The standard leads show RS-T displacement identical with that obtained during the first paroxysm. The unipolar limb leads also show RS-T displacement, although it was not recorded in these leads during the previous seizure. After correction for standardization, the unipolar chest leads exhibit slight reduction in the amplitude of the T waves in Lead V_1 , moderate reduction in Leads V_2 and V_3 , slight increase in Leads V_4 , V_5 , V_6 , and V_7 , and no change in Lead V_8 .

An intracutaneous test, using extracts of tobacco of ten popular brands of cigarettes, produced a wheal approximately 1 cm. in diameter and without pseudopodia. This reaction was interpreted by Dr. Oscar Swineford as being of questionable significance.

The patient was informed of the significance of the foregoing observations, but he was not convinced that his symptoms were precipitated by smoking. While driving home he smoked six cigarettes and experienced the same discomfort each time. Finally, having convinced himself that his seizures were induced by smoking, he ceased smoking altogether.

In a letter dated March 13, 1945, he wrote: "In spite of doing everything that you told me not to do except smoking, I have just gotten along fine, haven't had a pain. Work sixteen hours a day, eat irregular, pull the mountains or stairsteps with no discomfort whatever."

CASE 2.—A passenger train conductor, aged 62 years, was first seen as an outpatient on May 29, 1944. Six months previously he noted for the first time a squeezing substernal sensation associated with choking and pain at the angles of both jaws. It occurred in the evening when he was walking up a slight incline on his way home from work. This discomfort would promptly subside with rest or if he took nitroglycerin. In the succeeding months it appeared at more frequent intervals and was precipitated by progressively smaller amounts of exercise. Dyspnea did not accompany these episodes of pain. Large meals decreased the amount of exercise required to induce them. Approximately four weeks before he came under observation, the symptoms, previously associated only with exertion, began to appear regularly just after he lay down in bed at night and made it necessary for him to sit up or to take nitroglycerine for relief. The patient was not aware of any relation between smoking and the onset of discomfort.

His only other complaint was long-standing "gaseous indigestion" after meals. This symptom was relieved by belching initiated by sodium bicarbonate. He also stated that he had been informed a number of years previously that he had "high blood pressure." Nocturia of two or three times was present.

On examination, the heart was of normal size, a soft systolic murmur was present at the apex, and there was slight accentuation of the aortic second sound. The blood pressure was 159/70. The peripheral arteris were markedly sclerotic and tortuous. The eye grounds were not unusual. The liver edge was 2 cm. below the right costal margin on inspiration but was not tender. The lung fields were clear on fluoroscopy. No dependent edema was present. Examinations of the urine and blood were normal. The Wassermann and Kahn tests were negative. Orthodiagnosis (Kurtz) showed that the area of the cardiac silhouette, in the frontal plane, was 15 per cent above the predicted normal for men of the patient's height and weight. This finding, however, was interpreted as within normal limits. There was a slight degree of dilatation of the thoracic aorta.

Routine electrocardiographic studies made with the subject recumbent and consisting of the classical leads, unipolar limb leads, and chest leads V_2 , V_4 , and V_6 were within normal limits. While still recumbent the patient was given a cigarette. Shortly after inhaling only a very few puffs he complained of severe squeezing substernal pain and of choking and aching at the angles of both jaws. The discomfort subsided in about ten minutes after he stopped smoking. Electrocardiographic tracings obtained while the discomfort was present show a slight increase in the heart rate, a decrease in the amplitude of the T waves, and depression of the RS-T segment, most pronounced in the chest leads.

After this information was obtained, the patient was again questioned as to the circumstances under which he usually experienced chest pain, and especially in regard to the effects of smoking. He stated that for several years he had been in the habit of smoking only two cigarettes a day, but these were consumed just before he retired at night. He insisted that he had never associated the chest discomfort with smoking.

On the following day, May 30, 1944, further electrocardiographic studies were carried out. Standard and unipolar limb leads, and unipolar chest leads from a series of points extending from the right sternal border around the left chest to the left scapular line, were within normal limits (Fig. 2). The subject then smoked his favorite brand of cigarettes while Lead V_5 was recorded continuously for two minutes and thereafter at two-minute intervals. This lead was chosen because it had shown the most pronounced changes on the previous day. A depression of the RS-T segment, measuring about 0.5 mm., was first noticeable one minute after the subject began to smoke (Fig. 3). However, chest discomfort did not appear until one minute later when the RS-T depression increased to 1.5 millimeters. The subject continued to smoke for twenty minutes, in spite of severe discomfort, and consumed several cigarettes. In addition to the symptoms previously described, he noted numbness of the right hand which occurred twenty minutes after he began to smoke. At this time he stopped smoking and 1/100 gr. of nitroglycerine was administered. The pain subsided gradually over the next thirteen minutes and ceased thirty-three minutes after it first came on. The RS-T depression in Lead V_5 increased to a maximum of 2.0 mm. approximately ten minutes after the onset of pain. The heart rate before smoking was 76 per minute. During the period of discomfort it varied between 84 and 94 per minute and, after the administration of nitroglycerine, it did not increase but gradually returned to the control level. No blood pressure readings were made.

A second complete set of tracings taken between twelve and twenty minutes after the beginning of the test shows changes identical with those exhibited by the curves of the previous day. It displays depression of the RS-T segment in Leads I, II, III, V_L , V_F , V_2 , V_3 , V_4 , V_5 , V_6 , V_7 , and V_B and elevation of this segment in Lead V_R . The voltage of the T waves decreased in Leads I and V_L and in all the chest leads but increased in Lead II. In Lead III the originally negative T waves became positive. Intracutaneous tests with tobacco extracts gave results similar to those obtained in Case 1.

The patient was seen for the last time in March, 1945. He had limited his activities and had discontinued the use of tobacco. He was taking aminophylline; nevertheless his attacks continued to occur with about the same frequency.

A patient previously reported by Wilson and Johnston^{2*} was recalled and was re-examined on July 11, 1946. This man, an attorney, now 57 years of age, developed angina pectoris in 1938. The paroxysms were not related to emotion or to exertion. They were most likely to occur when he had gone to bed at night. He obtained relief by standing up and by belching, which he often induced by taking sodium bicarbonate or nitroglycerine. He gave a history of gaseous indigestion from his twenty-fifth year. Studies carried out in February, 1939, showed transient electrocardiographic changes, precipitated by smoking, similar in magnitude and character to those observed in acute posterior myocardial infarction. These changes were not accompanied by subjective symptoms or by changes in the pulse rate or blood pressure. More pronounced changes of a similar kind were, however, recorded during an apparently spontaneous attack of anginal pain.

Although the patient had been advised to give up the use of tobacco, he continued to smoke an average of one package of cigarettes per day throughout the succeeding seven years. When seen in July, 1946, he stated that he had continued to have anginal attacks similar to those described, but had never noticed any relation between smoking and the onset of the paroxysms.

Electrocardiograms taken on July 11, 1946, showed only minor changes when compared with the routine tracings obtained in 1939. The T wave in Lead I had become diphasic and a small Q wave had appeared in Lead II. At this time the smoking of three cigarettes produced neither symptoms nor changes in the electrocardiograms, blood pressure, or heart rate.

*See their Case 5.

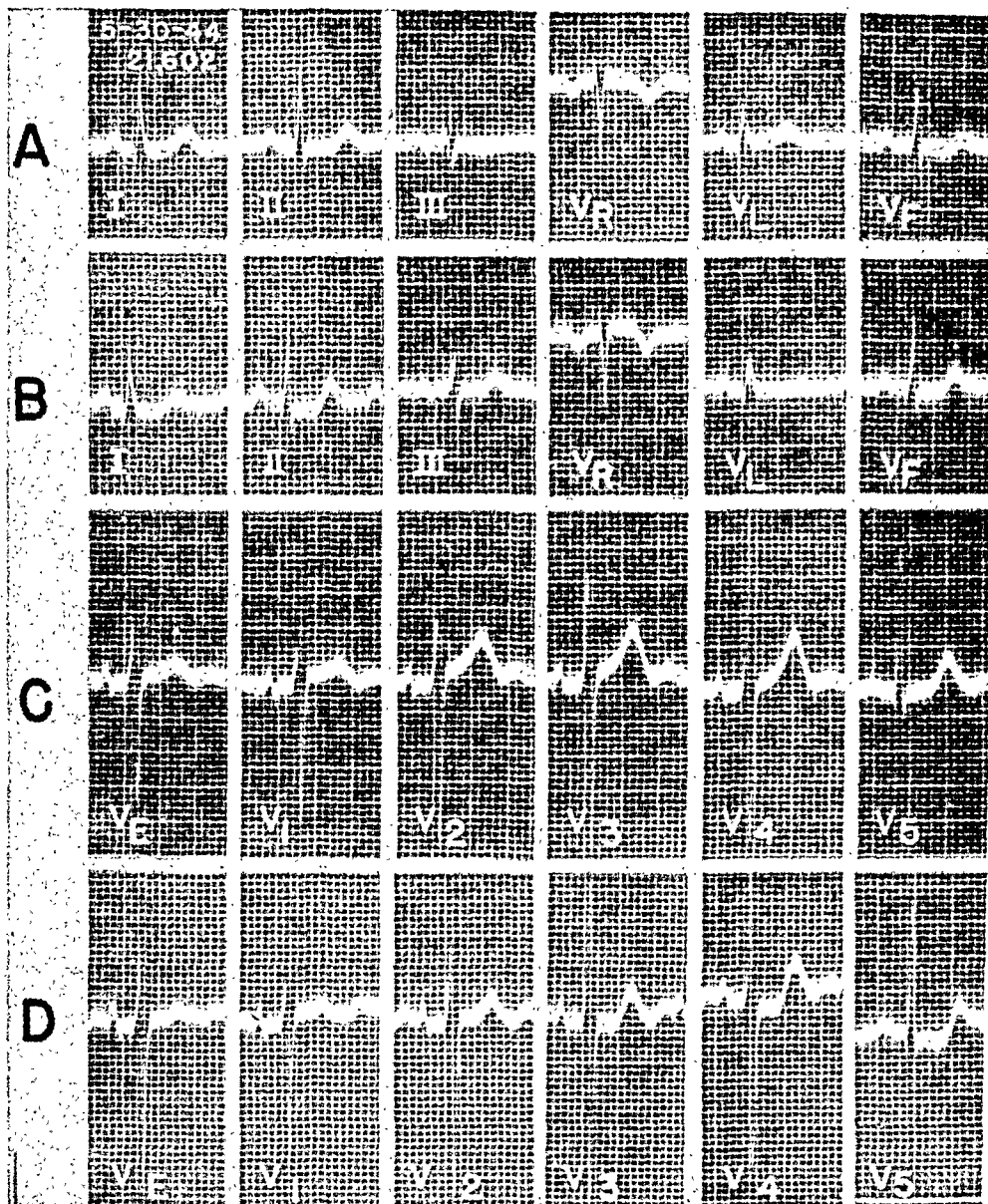


Fig. 2.—Case 2. Electrocardiograms taken before and during attack induced by smoking. A, Limb leads before and, B, during smoking. C, Unipolar chest leads before and, D, during smoking.

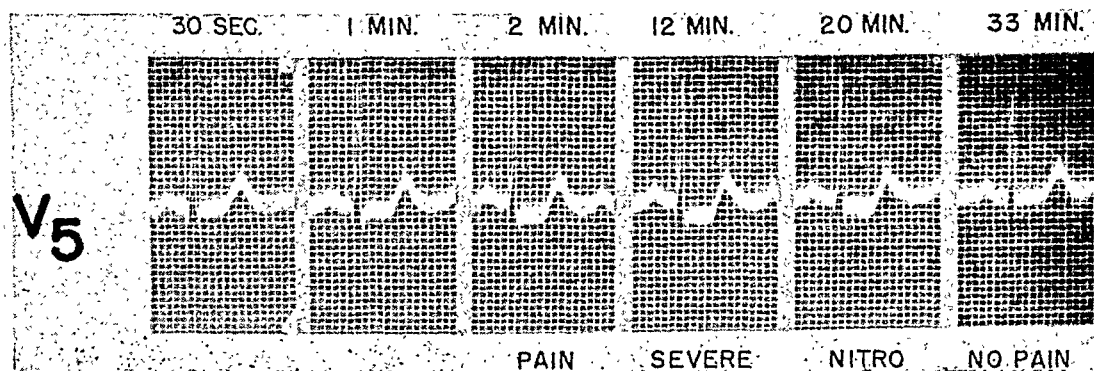


Fig. 3.—Case 2. Serial tracings of Lead V_5 taken before, during, and after anginal attack precipitated by cigarette smoking. No change from control (see Fig. 2, C) until one minute after subject began to smoke. Pain appeared two minutes after smoking started, right hand became "numb" at eighteen minutes, and subject ceased smoking and took 1/100 gr. nitroglycerin at twenty minutes; complete disappearance of pain 33 minutes after the subject began smoking.

DISCUSSION

Of the sixteen patients with angina pectoris on whom data are presented in this study, eleven showed an increase in heart rate and minor T-wave changes after smoking. The magnitude of the changes in the T wave was proportional to the increase in rate. Others^{20,63} have observed this relation which probably represents a normal physiologic response. It has been suggested that these T-wave changes are due to the direct action of nicotine on the heart muscle fibers,⁴¹ but we do not believe that there is much support for this view in the evidence available.

In two patients smoking induced the classical symptoms of angina pectoris accompanied by electrocardiographic changes diagnostic of pronounced myocardial ischemia.

Theoretical and experimental studies^{65,66} indicate that injury which affects chiefly or predominantly the subendocardial muscle gives rise to RS-T segment depression in the unipolar leads taken with the exploring electrode adjacent to the epicardial surface of the part of the ventricular wall involved, whereas subepicardial injury produces RS-T elevation under similar circumstances. In the case of the unipolar right arm lead (V_R), the exploring electrode faces the basal ventricular orifices and often seems to reflect the potential of the ventricular cavities. The ventricular complex of this lead is frequently almost the inverse of those obtained when the exploring electrode faces the epicardial surface. If the RS-T displacements in the standard leads are plotted on the Einthoven triangle, the resulting vector gives the manifest axis of injury ($-I$).^{67,68} When the injury is predominantly subepicardial, this axis points from the center of the involved ventricle toward the center of the injured area (Fig. 4). When the injury is predominately subendocardial it points in the opposite direction (Fig. 5).⁶⁸ Unfortunately, this type of analysis is complicated by a number of factors and possibilities that have not been fully developed. Some of these factors will be discussed at greater length in a subsequent paper.

When the electrocardiographic changes in Case 1 are analyzed by simple inspection of the unipolar limb leads or by the principles of the Einthoven triangle, the RS-T displacement suggests ischemia of the posteroseptal subepicardial muscle, which is irrigated by the right coronary artery (Fig. 4). The relatively minor changes in the T waves of the chest leads during the anginal attack were not accompanied by a change in heart rate. These changes probably reflect the influence of the ischemic area on the posteroseptal wall if it can be assumed that the same conditions were present when both the limb and chest leads were obtained. The failure of the heart rate to rise suggests that the work of the heart was not significantly increased during the paroxysm. Moreover, the absence of exertional heart pain supports the view, in this particular instance, that an increase in cardiac work was not the sole or even the chief factor inducing anginal seizures. It seems necessary to assume that the series of events described were a consequence of spasm of the right coronary artery or its branches.

In Case 2 there was concordant RS-T displacement without significant QRS changes during the anginal paroxysms precipitated by smoking. This suggests

a more widespread ischemia. Leads in which the exploring electrode faced the epicardial surfaces of the ventricles show RS-T depression, whereas in the unipolar right arm lead (V_R), which often reflects the potential variations of the ventricular cavities, there is RS-T elevation (Fig. 2). The axis of injury points

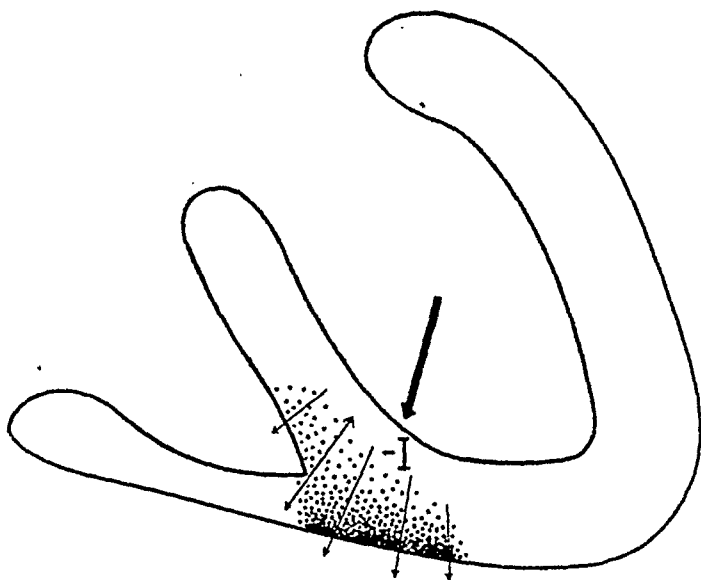


Fig. 4.—Case 1. Diagram representing hypothetical location of predominate myocardial ischemia induced by smoking and axis of injury ($-I$).

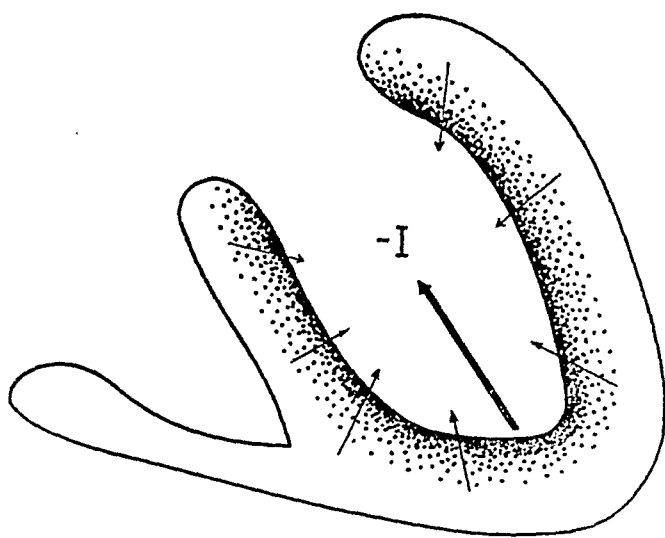


Fig. 5.—Case 2. Distribution of hypothetical ischemic region indicated by shaded area. Position of axis of injury ($-I$) during anginal seizure precipitated by smoking.

from the apex toward the center of the left ventricle (Fig. 5). These findings are consistent with uniform ischemia of the greater portion of the subendocardial muscle of the left ventricle. Such changes may be the result of generalized coronary spasm or spasm of the subendocardial arteriolar plexus.

Concordant RS-T segment depression in the standard leads is the most frequent electrocardiographic phenomenon accompanying anginal attacks induced by exercise⁶⁹ and anoxemia.⁷⁰ The majority of the relatively few electrocardiograms that have been taken during spontaneous anginal seizures show a discordant type of RS-T displacement.^{2,54,69,71-73}

The follow-up on Wilson and Johnston's Case 5² is presented to show that in a case of proved tobacco angina the patient may lose his sensitivity to tobacco and still continue to experience pain unrelated to exercise.

It is interesting to note that all the patients who exhibited striking electrocardiographic changes on smoking had complained of "gaseous indigestion," suggestive of peptic ulcer, for a long time prior to the development of angina pectoris. This was also true of the two patients of Wilson and Johnston.² The possibility that there is a relation between diseases of the coronary arteries and the abdominal viscera has received considerable attention in the past few years.⁷⁴ Since both myocardial infarction and peptic ulcer have been produced in experimental animals by vagal stimulation,⁶⁰ it may be that these two conditions have one etiologic factor in common.

We wish to emphasize that in an unselected group of sixteen patients with angina pectoris, two habitual cigarette smokers with no previous suspicion of tobacco sensitivity developed typical anginal seizures accompanied by electrocardiographic changes indicating severe myocardial ischemia while smoking their usual brand of cigarettes. The evidence points to spasm of some part of the coronary arterial tree as the mechanism through which smoking induced paroxysms in these two patients. However, these findings by no means rule out the probability that in other patients smoking may precipitate attacks of angina pectoris by increasing the work of the heart.

In our experience, the clinical history and the clinical data routinely collected rarely suggests that smoking has an important bearing upon the symptoms in the course of the patient's illness in angina pectoris and other forms of coronary artery disease. But the circumstances which led to the discovery of a relation between the anginal attacks and the use of tobacco in two patients of this series and in two patients studied by Wilson and Johnston² suggest the possibility that this habit may play a more important role in these disorders than has been suspected heretofore. Routine smoking tests with electrocardiographic observations on patients with angina pectoris, even in the absence of a history of tobacco sensitivity, may help to decide this question.

CONCLUSIONS

1. In sixteen patients with angina pectoris, electrocardiograms were taken while the patient was smoking cigarettes of the brand to which he was accustomed. One instance of pure tobacco angina was discovered. In another instance the pain was precipitated by exertion and by tobacco. Neither patient had suspected that his symptoms were in any way related to smoking.

2. In these instances coronary spasm induced by smoking appeared to be the cause of the anginal seizures not related to exertion.

3. Minor changes in the T wave induced by smoking usually represent a physiologic response to an increase in the heart rate and not to myocardial ischemia. This phenomenon occurs in patients with angina pectoris as well as in normal subjects but is not associated with anginal pain.

4. The cardiovascular effects of tobacco smoking vary greatly from person to person and in the same person from time to time.

5. It is possible that the use of tobacco plays a more important role in determining the symptoms of coronary disease than has been realized in the past.

The authors wish to express their appreciation to Dr. Frank N. Wilson for his help in the preparation of this paper.

REFERENCES

1. Huchard, H.: *Traité clinique des maladies du coeur et de l'aorte*, ed. 3, Paris, 1899, Gaston Doin & Cie, vol. 2.
2. Wilson, F. N., and Johnston, F. D.: The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and in Kind to Those Produced by Myocardial Infarction, *Tr. A. Am. Physicians* 54: 210, 1939.
3. White, P. D.: *Heart Disease*, ed. 3, New York, 1945, The Macmillan Co.
4. Levine, S. A.: *Clinical Heart Disease*, ed. 3, Philadelphia, 1945, W. B. Saunders Co.
5. Pickering, G. W., and Sanderson, P. H.: Angina Pectoris and Tobacco, *Clin. Sc.* 5: 275, 1945.
6. Allbutt, C.: *Diseases of the Arteries Including Angina Pectoris*, ed. 1, London, 1915, Macmillan & Co., Ltd.
7. Gallavardin, L.: *Les angines de poitrine*, ed. 1, Paris, 1925, Masson & Cie.
8. Willson, R. N.: The Effects of Tobacco and Alcohol Upon the Cardiovascular System, *New York M. J.* 102: 541, 1915.
9. Ralli, E. P., and Oppenheimer, B. S.: Changes in the Peripheral Circulation Accompanying "Tobacco Angina," *Proc. Soc. Exper. Biol. & Med.* 26: 9, 1928.
10. Moschocowitz, E.: Tobacco Angina Pectoris, *J.A.M.A.* 90: 733, 1928.
11. Golston, H.: The Tobacco Heart, *Virginia M. Monthly* 64: 319, 1937.
12. Birk, B. J., and Huber, H. H.: Angina Pectoris and Tobacco Smoking, *Wisconsin M. J.* 38: 733, 1939.
13. Maddock, W. G., and Collier, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, *Ann. Surg.* 98: 70, 1933.
14. Barker, N. W.: Vasoconstriction Effects of Tobacco Smoking, *Proc. Staff Meet., Mayo Clin.* 8: 284, 1933.
15. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral Vascular System, *J.A.M.A.* 103: 318, 1934.
16. Maddock, W. G., Malcolm, R. L., and Collier, F. A.: Thrombo-Angiitis Obliterans and Tobacco: the Influence of Sex, Race and Skin Sensitivity to Tobacco on Cardiovascular Responses to Smoking, *AM. HEART J.* 12: 46, 1936.
17. Shulman, I., and Mulinos, M. G.: The Factors Concerned in the Vasoconstriction From Tobacco Smoking, *Am. J. Physiol.* 126: 629, 1939.
18. Weatherby, J. H.: Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, *AM. HEART J.* 24: 17, 1942.
19. Roth, G. M., McDonald, J. B., and Sheard, C.: The Effect of Smoking Cigaretts and of Intravenous Administration of Nicotine on Electrocardiogram, Basal Metabolic Rate, Cutaneous Temperature, Blood Pressure and Pulse Rate of Normal Persons, *J.A.M.A.* 125: 761, 1944.
20. Evans, W. F., and Stewart, H. J.: The Effect of Smoking Cigarettes on the Peripheral Blood Flow, *AM. HEART J.* 26: 78, 1943.
21. Goetz, R. H.: Smoking and Thrombo-Angiitis Obliterans, *Clin. Proc.* 1: 190, 1942.
22. Short, J. J., and Johnson, H. J.: A Direct Comparison of the Reactions of the Human System to Tobacco Smoke and Adrenalin, *J. Lab. & Clin. Med.* 24: 590, 1939.
23. Harkavy, J., Hebal, S., and Silbert, S.: Tobacco Sensitiveness in Thrombo-Angiitis Obliterans, *Proc. Soc. Exper. Biol. & Med.* 30: 104, 1932.
24. Sulzberger, M. B.: Studies in Tobacco Hypersensitivity. I. A Comparison Between Reactions to Nicotine and Denicotinized Tobacco Extract, *J. Immunol.* 24: 85, 1933.
25. Westcott, F. H., and Wright, I. S.: Tobacco Allergy and Thrombo-Angiitis Obliterans, *J. Allergy* 9: 555, 1938.
26. Moyer, C. A., and Maddock, W. G.: Peripheral Vasospasm From Tobacco, *Arch. Surg.* 40: 277, 1940.

27. Sollman, T.: *A Manual of Pharmacology and Its Application to Therapeutics and Toxicology*, ed. 6, Philadelphia, 1942, W. B. Saunders Co.
28. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, ed. 1, New York, 1941, The Macmillan Co.
29. Laubry, C., Walser, J., and Deglaude, L.: Action expérimentale du tabac et de la nicotine sur le débit coronarien, *Bull. Acad. de méd., Paris* 109: 595, 1933.
30. Mansfield, G., and Hecht, K.: Untersuchungen über die Wirkung des Tabakrauchens auf das Herz-Lungenpräparat von Hunden, *Arch. f. exper. Path. u. Pharmacol.* 172: 362, 1933.
31. Meyer, F.: Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefäße des lebenden Tieres, *Arch. f. Anat. u. Physiol. Abt.*, p. 223, 1912.
32. Glendy, R. E., Levine, S. A., and White, P. D.: Coronary Disease in Youth, *J.A.M.A.* 109: 1775, 1937.
33. English, J. P., Willius, F. A., and Berkson, J.: Tobacco and Coronary Disease, *J.A.M.A.* 115: 1327, 1940.
34. Pearl, R.: Tobacco Smoking and Longevity, *Science* 87: 216, 1938.
35. Thienes, C. H., and Butt, E. M.: Chronic Circulatory Effects of Tobacco and Nicotine, *Am. J. M. Sc.* 195: 522, 1938.
36. Bellet, S., Kershbaum, A., Meade, R. H., Jr., and Schwartz, L.: The Effects of Tobacco Smoke and Nicotine on the Normal Heart and in the Presence of Myocardial Damage Produced by Coronary Ligation, *Am. J. M. Sc.* 201: 40, 1941.
37. Weinroth, L. A., and Herzstein, J.: Relation of Tobacco Smoking to Arteriosclerosis Obliterans in Diabetes Mellitus, *J.A.M.A.* 131: 205, 1946.
38. Silbert, S.: Etiology of Thrombo-Angiitis Obliterans, *J.A.M.A.* 129: 5, 1945.
39. Ssalischtscheff, A. S., and Tschernogoroff, J. A.: Elektrokardiographische Analyse der Nicotinwirkung auf das Herz, *Ztschr. f. d. ges. exper. Med.* 64: 319, 1929.
40. Segal, H. L.: Cigarette Smoking; I. As a Cause of Fatigue; II. Effect on the Electrocardiogram With and Without the Use of Filters, *Am. J. M. Sc.* 196: 851, 1938.
41. Graybiel, A., Starr, R. S., and White, P. D.: Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, *AM. HEART J.* 15: 89, 1938.
42. Johnson, H. J., and Leslie, C. J.: The Effect of Tobacco Smoke on the Normal Electrocardiogram, *Proc. Life Ext. Exam.* 3: 27, 1941.
43. Grollman, A.: The Action of Alcohol, Caffeine, and Tobacco on the Cardiac Output (and Its Related Functions) of Normal Man, *J. Pharmacol. & Exper. Therap.* 39: 313, 1930.
44. Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram With Particular References to T-Wave Changes, *J. Clin. Investigation* 21: 409, 1942.
45. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient. II. Factors Which Affect Its Relationship to the Manifest Area of the QRS Complex, *AM. HEART J.* 25: 36, 1943.
46. Ashman, R., Ferguson, F. P., Gremillion, A. I., and Byer, E.: The Effect of Cycle Length Changes Upon the Form and Amplitude of the T-Deflection of the Electrocardiogram, *Am. J. Physiol.* 143: 453, 1945.
47. Dameshek, W., Loman, J., and Myerson, A.: Human Autonomic Pharmacology. VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmine, Benzedrine—With Especial Reference to the Electrocardiogram, *Am. J. M. Sc.* 195: 88, 1938.
48. Lewis, T.: *Diseases of the Heart*, ed. 2, New York, 1937, The Macmillan Co.
49. Roth, G.: The Effects of Smoking Tobacco on the Cardiovascular System, Part I, *Modern Concepts of Cardiovascular Disease*, vol. 14, no. 4, 1945, American Heart Association.
50. Heberden, W.: *Commentarii de morborum historia*. Cap. 70, De Dolore Pectoris, London, 1802, Thomas Payne.
51. Duke, W. W.: Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Function Cardiac Disorders Including Angina Pectoris, Tachycardia and Ventricular Extrasystoles, *J. Allergy* 4: 38, 1932.
52. Riseman, J. E. F.: The Relation of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris Precipitated by Effort, *AM. HEART J.* 12: 53, 1936.
53. Mackenzie, J.: *Angina Pectoris*, ed. 1, London, 1923, Henry Frowde, Hodder and Stoughton.
54. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, Their Bearing on the Origin of Anginal Pain, *Lancet* 1: 15, 1931.
55. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, *AM. HEART J.* 21: 634, 1941.
56. Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C.: The Electrocardiogram and the "Two Step" Exercise, *Am. J. M. Sc.* 207: 435, 1944.
57. Anrep, G. V.: *Lane Medical Lectures: Studies in Cardiovascular Regulation*, Stanford Univ. Publ., Univ. Series, M. Sc. 3: 199, 1936.

58. Wiggers, C. J.: The Physiology of the Coronary Circulation, in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, ed. 1, New York, 1936, The Macmillan Co., chap. 2.
59. Gregg, D. E.: The Coronary Circulation, *Physiol. Rev.* 26: 28, 1946.
60. Manning, G. W., Hall, G. E., and Banting, F. G.: Vagus Stimulation and the Production of Myocardial Damage, *Canad. M. A. J.* 37: 314, 1937.
61. Gilbert, N. C.: The Influence of Extrinsic Factors on the Coronary Flow and Clinical Course of Heart Disease, *Bull. New York Acad. Med.* 18: 83, 1942.
62. Leary, T.: Coronary Spasm as a Possible Factor in Producing Sudden Death, *AM. HEART J.* 10: 338, 1934.
63. White, P. D.: Discussion of Wilson and Johnston's paper,² *Tr. A. Am. Physicians* 54: 223, 1939.
64. Bryant, J. M., and Wood, J. E., Jr.: Recent Advances in Electrocardiography; an Earlier Objective Diagnosis of Angina Pectoris, *Virginia M. Monthly* 71: 562, 1944.
65. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Interpretation of the Galvanometric Curves Obtained When One Electrode is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface, *AM. HEART J.* 10: 163, 1934.
66. Pruitt, R. D., and Valencia, F.: Unpublished observations.
67. Bayley, R. H.: An Interpretation of the Injury and the Ischemic Effects of Myocardial Infarction in Accordance With the Laws Which Determine the Flow of Electric Currents in Homogenous Volume Conductors, and in Accordance With Relevant Pathologic Changes, *AM. HEART J.* 24: 514, 1942.
68. Bayley, R. H.: Personal communication.
69. Bryant, J. M., and Wood, J. E., Jr.: Unpublished observations.
70. Pruitt, R. D.: Personal communication.
71. Brow, G. R., and Holman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, *AM. HEART J.* 9: 259, 1933.
72. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
73. Wood, F. C., Wolferth, C. C., and Livezey, M. M.: Angina Pectoris, the Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* 47: 339, 1931.
74. Levy, H., and Boas, E. P.: Angina Pectoris and the Syndrome of Peptic Ulcer, *Arch. Int. Med.* 71: 301, 1943.

THE TECHNIQUE OF FETAL ELECTROCARDIOGRAPHY

SOLOMON HILLEL BLONDHEIM, M.D.
NEW YORK, N. Y.

INTRODUCTION

MODERN fetal electrocardiography is a highly successful and intriguing technique in search of useful clinical applications. Since the first successful series of cases was presented by Strassmann in 1938,¹ there have been a number of further reports. All the authors are enthusiastic over the relative ease of obtaining tracings of the fetal heart potentials, and many clinical applications have been suggested. Nevertheless, in the past four years there has been only one report of a series of fetal electrocardiograms in the English literature. The readily available and reliable procedures of auscultation of the fetal heart and x-ray of the maternal abdomen leave only a limited field of application for fetal electrocardiography. Furthermore, the records produced by the standard unmodified electrocardiograph may be difficult to read. Ward and Kennedy,² however, demonstrated that the electroencephalograph could be used without modification to record fetal deflections in a large percentage of cases. Although the electroencephalograph is now standard apparatus in many large hospitals, no further use of the method has been reported, either for routine series, or for study of the rare cases where electrocardiography alone can supply the needed obstetrical information.

The purpose of this report is (1) to present the second series of cases in which the electroencephalograph has been used to record the fetal electrocardiogram, (2) to suggest a standardized technique for fetal electrocardiography, (3) to review the literature on the characteristics of the fetal electrocardiogram and the problems involved in its recording, and (4) to evaluate the clinical applications of the technique.

METHOD

Twenty-five patients were selected at random from those attending an antepartum clinic. They were placed in the supine position, with a low pillow under the head. Standard electrocardiograph electrodes ($1\frac{1}{2} \times 2\frac{1}{2}$ inches) with the rubber straps removed were coated with electrode jelly and placed on the abdomen at sites that had been rubbed with electrode jelly. The electrodes were held in place with six inch strips of adhesive tape. The positions of the electrodes were the right and left upper quadrants and the midline at the superior

From the Department of Obstetrics, Lenox Hill Hospital.
Received for publication Sept. 25, 1946.

limits of the uterus, and the suprapubic region just above the pubic escutcheon. These electrodes were led into the terminals of a four channel push-pull amplifier type electroencephalograph by means of the usual fine electroencephalograph electrode connection wires. The three leads used routinely and recorded simultaneously were right upper quadrant to suprapubic region, midline upper abdomen to suprapubic region, and left upper quadrant to suprapubic region. The polarity was such that when the superior electrode was negative with respect to the inferior electrode, an upright deflection was recorded. The patient was allowed to rest quietly after adjustment of the electrodes for about five minutes, and then the record was standardized and recording begun. If inspection of the tracing as it was being recorded failed to reveal readily apparent fetal deflections, the placement and connections of the electrodes were rechecked, and the recording was continued intermittently at two to three minute intervals with increasing amplification. After about ten minutes the tracing was discontinued.

Frequently tracings that appear negative on casual inspection reveal small deflections, consistent in direction, shape, and spacing, amid the irregular variations in the baseline caused by artifacts. Small fetal deflections are most readily detected when they are superimposed upon the maternal P and T waves, and thus alter the contour of the maternal waves.

RESULTS

A total of twenty-eight tracings was taken on twenty-five women in the last five lunar months of pregnancy. Of these records, twenty-three, or 82 per cent, were positive, while one tracing was doubtful, and four tracings were negative for fetal deflections. One patient delivered as a breech one week after the recording of upright fetal deflections (Fig. 1). One record showed two independent sets of fetal deflections in a proven case of twins (Fig. 2).

The fetal and maternal heart rates were measured at the beginning and end of each tracing and were found to vary independently. In twelve cases, one heart slowed while the other increased in rate; in eight cases both maternal and fetal heart rates increased or decreased together; in four cases only a single measurement of rate could be made. The sex of the fetus had no effect on the heart rates. The average rate for males (fifteen cases) was found to be 142 and the average rate for females (nine cases) was 143. The average change in rate from beginning to end of the tracing for males was 11 beats per minute, while that for females was 14 beats. No significant change in the rate of the fetal heart was observed during the course of the last five lunar months of pregnancy.

Except for moderate degrees of sinus arrhythmia, no unusual rhythms were noted. Smoking produced showers of premature beats in one patient, but had no effect on the fetal heart other than a very slight increase in rate.

The average voltage of the fetal deflections was found to be 7 microvolts. In no tracing was there any significant increase in the duration of the fetal deflection beyond 0.04 second.

The height-weight ratio (height in inches divided by normal weight in pounds) was determined for women in the sixth to eighth months. Eight women

with positive tracings had an average ratio of 0.48 while five women with negative tracings had an average ratio of 0.47. Although these groups are very small, it does not appear that bodily habitus was an important factor in determining the incidence of negative tracings.

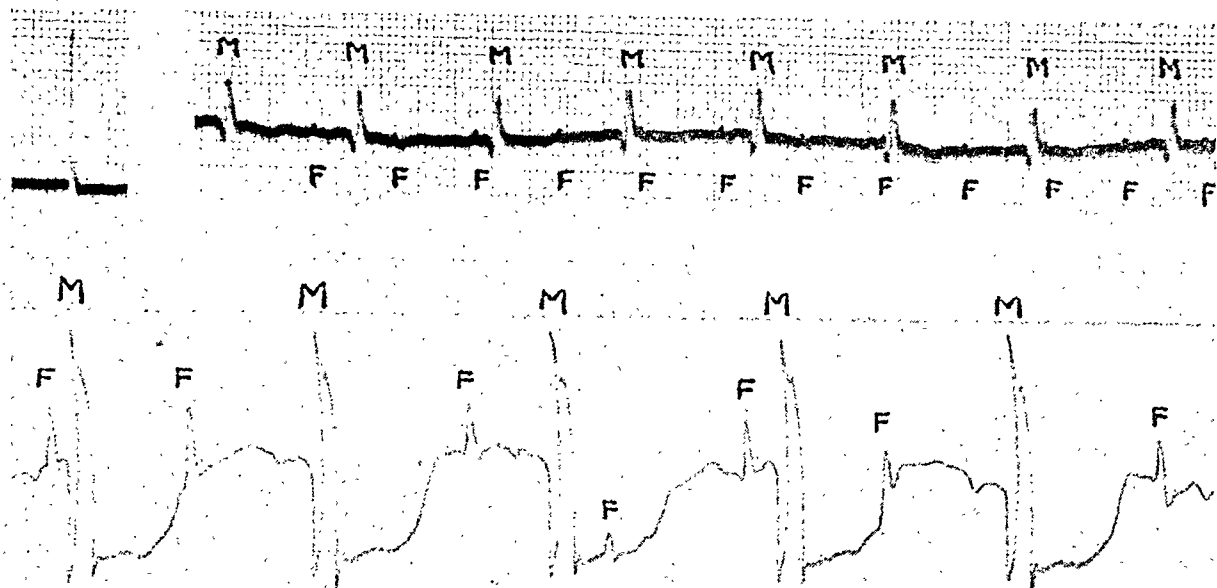


Fig. 1.—Breech presentation.

Tracings taken at term from a woman whose x-ray film showed a breech presentation and who delivered as a breech seven days later.

Upper tracing taken with standard electrocardiograph with approximately double standardization. Upright fetal deflections measure less than 1.0 millimeter.

Lower tracing taken with electroencephalograph from the same electrodes shows fetal deflections measuring 8.0 mm.

M represents maternal deflections and *F* the fetal deflections.

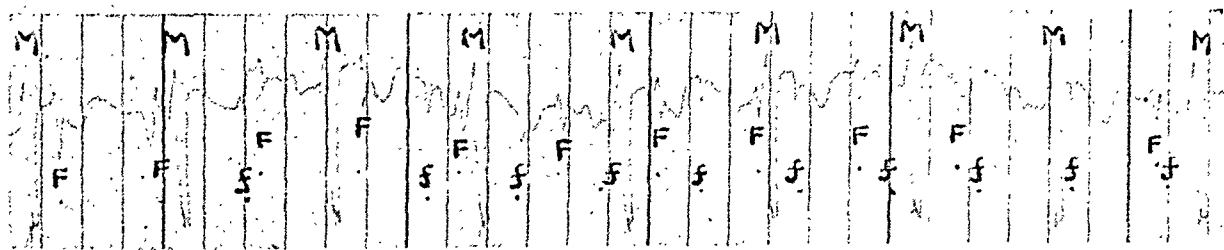


Fig. 2.—Tracing of twins.

Tracing shows two independent sets of fetal deflections. *M* indicates maternal deflections (QRS) while *f* indicates monophasic fetal deflections, downward directed, of a vertex presentation. *F* indicates diphasic fetal deflections with initial positive wave indicating breech presentation.

X-ray taken fifteen minutes after the tracing showed twins, one a breech and the other a vertex. The patient delivered a breech and a vertex three days later.

DISCUSSION

The various series of fetal electrocardiograms reported in the literature differ widely in many details of technique. Analysis of these variations shows that the simplest procedures apparently yielded the best results. This is fortunate, for if fetal electrocardiography is to be used clinically in the study of the infrequent cases in which it alone can yield valuable information, a simple and easily applied technique must be available.

Standardization of Technique.—

1. *Recording Instrument:* Specially designed recording apparatus is not readily available to the obstetrician. Such apparatus includes the valve amplifier used with the string galvanometer by Maekawa and Toyoshima,³ the balanced input amplifier introduced into the circuit of a valve electrocardiograph used by Bell,⁴ the specially designed "Cardiette" with a sensitivity of 6 cm. per millivolt used by Bernstein and Mann,⁵ and the single stage resistance-coupled preamplifier used by Goodyer, Geiger, and Monroe.⁶ In many large hospitals, however, the standard electroencephalograph apparatus is available for routine use. This type of apparatus has a far greater sensitivity than the most powerful of the specially designed equipment, giving an indicated deflection of up to 100 cm. per millivolt. In 1942, Ward and Kennedy² demonstrated the ready application of the electroencephalograph to fetal electrocardiography. Lindsley⁷ had previously used this type of apparatus in a single case in 1936, but did not publish his report until 1942. The series reported in this communication was begun before these two papers were noted and was completed in 1943.

While the electroencephalograph is the most sensitive standard instrument available, the standard electrocardiograph, adjusted to normal,^{1,8} double,⁹ or triple¹⁰ standardization, has been used to record the fetal electrocardiogram. Only in the last two or three months of pregnancy, however, can the electrocardiograph be used with any degree of success. The superiority of the electroencephalograph over the electrocardiograph with approximately double standardization (1.7 cm. per millivolt) is shown in Fig. 3. The fetal deflections are much larger, clearer, and therefore easier to identify. The mechanical inertia of the pens tends to smooth out irregularities in the baseline produced by artifacts. The recording of all leads simultaneously shortens the procedure and allows for more certain identification of very small deflections by comparison of two or more leads. Furthermore, since the record is produced by ink-writers on paper, the results of the test are immediately available, and for special purposes long recordings may be made at little cost.

2. *Selection of Leads:* The early workers used rectal or vaginal leads in conjunction with abdominal leads.¹¹⁻¹³ This was later followed by the use of the standard limb leads taken from the proximal portions of the extremities.¹ Bell⁴ and Mann and Bernstein⁹ found that leads taken directly from the maternal abdomen were superior to limb leads, since such leads gave fetal deflections of larger amplitude, with maternal deflections reduced in amplitude, so that the sensitivity of the recording device could be increased. Fig. 3 shows this superiority of abdominal over limb leads. Most of the more recent series have been recorded from abdominal leads.

The location of the abdominal electrodes have varied in the different reports. Almost all authors have used a vertical lead from the epigastrium or umbilical region to the symphysis or suprapubic region. Diagonal leads have been taken from the epigastrium to the lower quadrants, from the upper quadrants to the suprapubic region, or from the upper quadrants to the diagonally opposite lower

quadrants. Transverse abdominal leads have also been used. The vertical and two diagonal leads are all necessary, for as shown by Goodyer and associates⁶ fetal deflections may appear in only one of these three leads. His use of the diagonal leads, from one upper quadrant to the opposite lower quadrant, is logical, since the greater angle between those leads and the vertical lead increases the likelihood of picking up weak potentials from longitudinal or near-longitudinal presentations. The superior electrodes should be placed at the upper limits of the uterus as determined by palpation. The lower midline electrode should be placed just above the pubic hairline to insure good contact. Abdominal leads should be referred to by letter, rather than designated "Lead I," which may be confused with the standard limb leads.

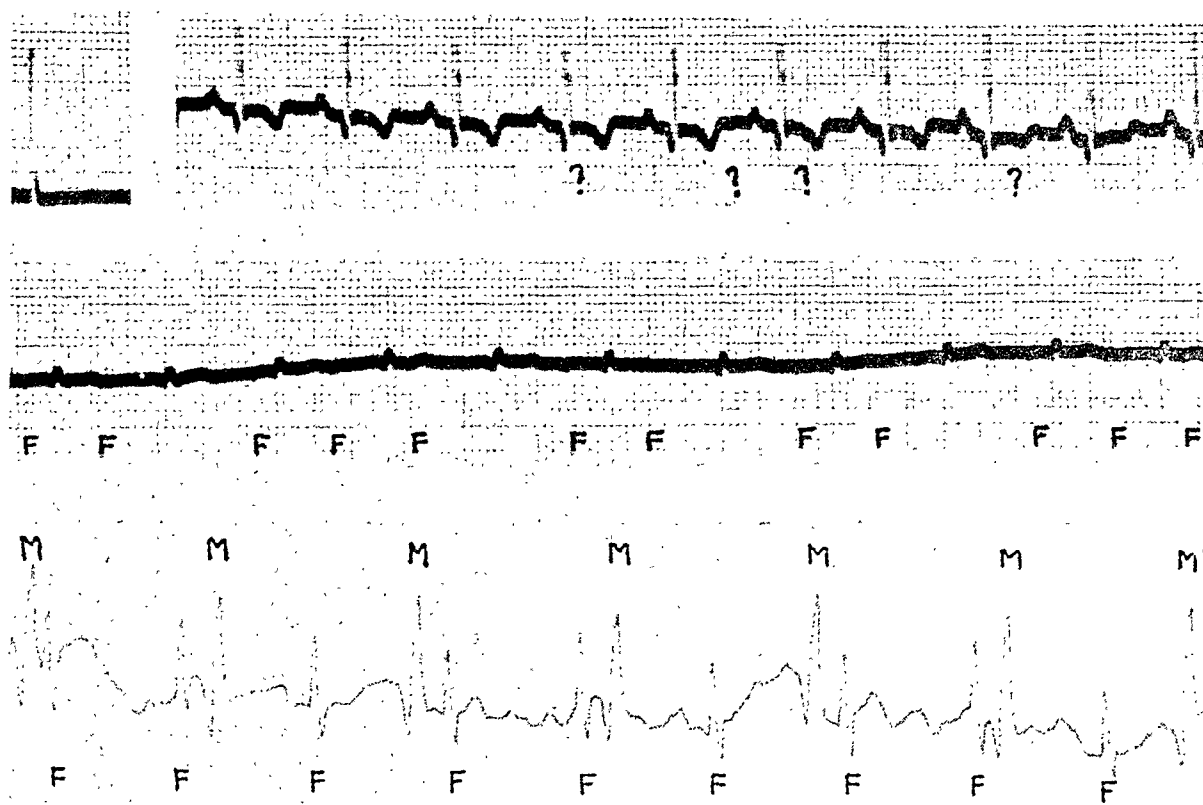


Fig. 3.—Comparison of leads and recording apparatus.

Top tracing taken with electrocardiograph at double standardization using standard limb Lead II, with electrodes at proximal portions of the limbs. A few irregularities are present in the baseline that cannot be positively identified as fetal deflections.

Middle tracing taken with electrocardiograph at approximately double standardization using abdominal leads. Tiny fetal deflections are visible that recur at regular intervals when not hidden by the maternal complexes.

Bottom tracing taken with electroencephalograph from same abdominal electrodes as middle tracing. Waves are altered in contour due to pen inertia. Fetal deflections are large, and the initial positive wave indicates a breech presentation, but no x-ray was available for confirmation. Patient was in sixth lunar month, and delivered at term as a vertex.

These tracings indicate the superiority of abdominal over limb leads, and of the electroencephalograph over the electrocardiograph for recording fetal electrocardiograms.

Lindsley⁷ pointed out that by varying the placement of the electrodes, it is possible to eliminate the maternal deflections from the record. This is confirmed in the tracing shown in Fig. 4. There is a progressive diminution in the

amplitude of the maternal deflection as the superior midline electrode is brought closer to the suprapubic electrode. The lowest pen records only the fetal deflections, with no maternal deflections identifiable. There is no advantage to be gained by eliminating the maternal complexes. In fact the maternal complexes are needed in order to prove the fetal origin of waves that might otherwise be mistaken for unusually small and rapid maternal deflections.

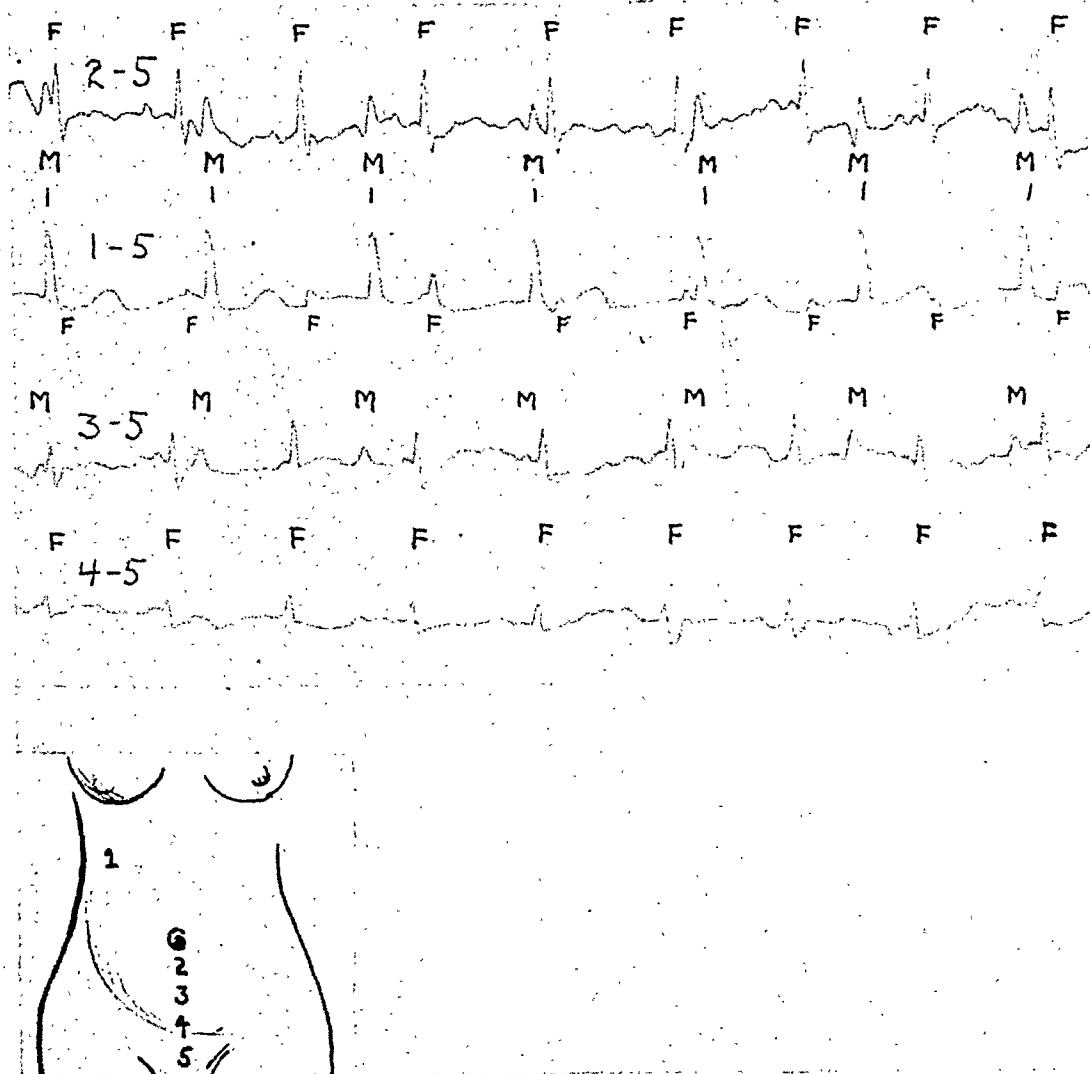


Fig. 4.—Elimination of maternal deflections.

The pens record four leads simultaneously. The location of the electrodes is illustrated in the diagram.

The second pen records from Position 1 to Position 5, one of the three routine abdominal leads. Large maternal and small fetal deflections are indicated by *M* and *F*, respectively.

The first pen records from Position 2 to Position 5, and shows the fetal deflections larger than the maternal.

The third pen records from Position 3 to Position 5, the superior electrode approaching the fixed interior electrode. Maternal deflections made out with difficulty.

The fourth pen, recording from Position 4 to Position 5 shows only fetal deflections, with maternal waves indistinguishable from baseline irregularities.

Lindsley's explanation for the blanking out of the maternal deflections is that the linea alba and aponeuroses of the abdominal muscles shunt the maternal currents. A more likely explanation is the negligible drop in potential of the maternal current taken over a short distance so far from the point of origin. At the same location, however, the electrodes are much closer to the origin of the fetal current, which shows a large drop in potential over a short distance.

3. *Minor Points of Technique:* Alteration in the time constants of the electroencephalograph used by Ward and Kennedy,² and increase in the paper speed in the string galvanometer used by Strassmann¹⁰ have been suggested as means of increasing the incidence of positive results. Having the patient void before the test eliminates the possibility of a full bladder short-circuiting the fetal potentials. Use of the supine position with a low pillow under the head eliminates much tremor due to contraction of the abdominal musculature. Most workers advise a short period of rest before recording is started. Frequently the fetal deflections can be found only near the end of the tracing when artifacts due to somatic tremor and other causes diminish.

The standard electrodes used in electrocardiography are readily applicable to this technique and are easily held in place by strips of adhesive tape. Electrode jelly, used in electrocardiography, is rubbed on the abdomen and spread on the electrodes, and gives results as good or better than saline dressings, which are less convenient.

The Fetal Electrocardiogram.—Although the fetal electrocardiogram as recorded by direct leads from aborted fetuses closely resembles the adult pattern,¹⁴⁻¹⁶ prenatal fetal electrocardiograms, recorded from the maternal abdomen or uterus,¹⁷ show only the initial ventricular deflections or QRS waves. The value of fetal electrocardiography in the diagnosis of fetal arrhythmias is thus almost nullified by the absence of recorded P waves.

Fetal deflections consist of either a single sharp spike (Fig. 5) or low curve if small, or of diphasic waves (Fig. 3). One tracing recorded by Ward and Kennedy² and another by Putz and Ulrich¹⁸ show complexes consisting of three components: a short positive wave followed by a deep negative spike, and then a short positive wave. The most variable of the factors governing the direction as well as amplitude of the fetal deflection is probably the position of the fetus in the uterus, or more concisely, the position of the fetal heart with respect to the electrodes recording the deflections. It has been assumed that when the superior electrode is negative with respect to the inferior electrode and an upright fetal deflection is inscribed, the position of the heart is base uppermost and apex pointing downward, or a breech presentation. Breeches have been diagnosed by this means, and one worker claims that "the most accurate method of detecting presentation is by means of a positive electrocardiogram."⁸ Strassmann and Mussey¹⁹ noted that frequently the initial negative deflection of vertex presentations is followed by a short positive deflection, while in breeches, the initial positive deflection is often followed by a short negative deflection. However, there are other factors affecting the fetal electrical axis that by the same token affect the direction as well as amplitude of the recorded deflections. These

include the relative size of the two sides of the heart, the difference in contraction timing between the two sides, and the position of the heart inside the fetal thorax. The full description of the recorded fetal complexes and their significance awaits careful study with a sensitive recording apparatus such as the electroencephalograph, in conjunction with x-ray examination and a study such as Bell performed⁴ consisting of a series of crown-rump leads on the newborn infants.

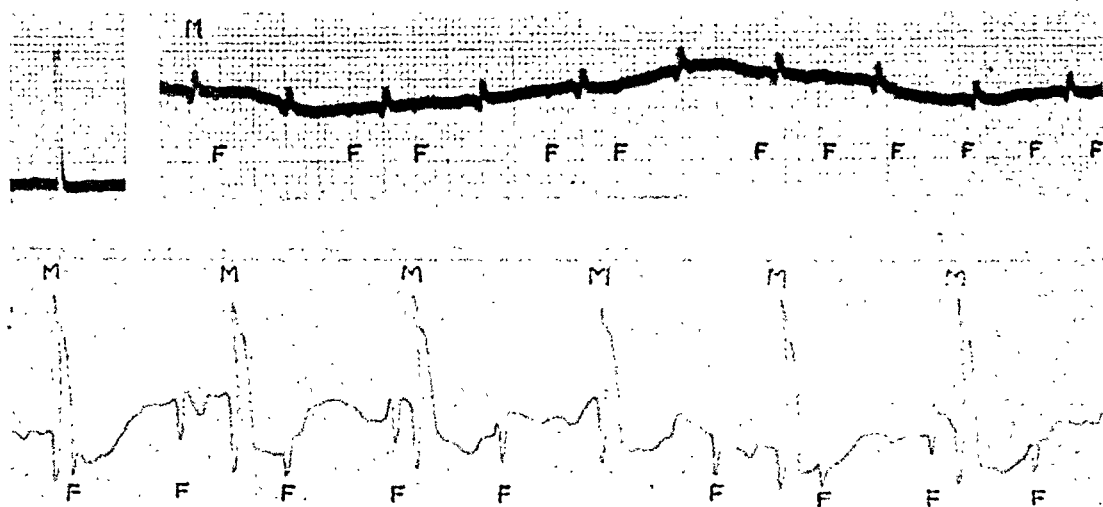


Fig. 5.—Vertex presentation.

Upper tracing taken with electrocardiograph at approximately double standardization using abdominal leads. Fetal deflections measure 0.5 millimeter.

Lower tracing taken with electroencephalograph from same electrodes. Fetal deflections measure up to 6.0 millimeters.

The amplitude of the fetal deflections obtained by Ward and Kennedy² averaged 30 microvolts. Goodyer⁶ recorded the largest fetal deflections of 70 microvolts. In this study the waves averaged only seven microvolts. Extracardiac factors that may influence the amplitude of the fetal deflections are the varying thickness of the abdominal wall and the other structures, and conducting media between the fetus and the electrodes. Even more important, however, is the angle between the electrodes and the axis of the fetus. The duration of the fetal deflections varies between 0.02 and 0.04 second.

It is known that marked variations in fetal rate occur without apparent cause, and that the rate is increased by fetal movement, palpation of the fetal body, fasting, asphyxia, and hemorrhage.²⁰ Fever,²¹ vibratory stimuli and loud sounds,²² smoking,²³ and inhalation of amyl nitrite by the mother²⁴ also increase the rate, while uterine contractions and pressure on the fetal brain²⁰ decrease the rate. The effect of other drugs on the human fetal heart has apparently not been systematically determined, although fetal electrocardiography offers an ideal technique for such studies.

Although a recent textbook of obstetrics states that "experience does seem to show that girls' (fetal) hearts beat faster than boys,"²⁰ none of the workers.

with fetal electrocardiography or stethography have been able to demonstrate such a difference.

The relationship of the fetal rate to fetal age has not been definitely determined. Sontag and Richards²⁵ and Sontag and Newberry²⁶ reported a gradual decline in the fetal rate from the fifth month to the tenth month, save for a slight rise in the ninth month. Bernstein and Mann,⁵ using the electrocardiograph, reported a gradual decline in the rate from the fourth to the eighth month, with a slight rise during the last two months of pregnancy. Goodyer⁶ was unable to find any correlation between fetal rate and age.

While many workers have claimed that the fetal rate is related to the maternal rate in various constant ratios, more recent reports have been unable to confirm this.^{5,6} The very great variability in the fetal rate from hour to hour²² compared with the relatively constant rate of the normal maternal heart at rest, would not seem to permit of the establishment of any such ratio. It has been shown in the foregoing that the fetal heart rate varied in inverse relationship to the rate of the maternal heart more often than in direct relationship.

In the analysis of fetal arrhythmias, the absence of P waves in the fetal electrocardiogram makes this method of no more value than fetal stethography. Fetal arrhythmias occur far more often than has been realized. Hyman²⁷ has stated that arrhythmias are present in over 9 per cent of pregnancies. So-called sinus arrhythmias are found very commonly. In view of the increasing evidence for fetal respiration,²³ this arrhythmia may well be similar to the sinus arrhythmia of postnatal life which is related to respiration. However, true sinus arrhythmia is mediated through the vagus, which does not exercise cardiac control until very late in fetal life.²⁹

Premature contractions, often identified as being of ventricular origin by postnatal electrocardiograms, have been described by many workers.^{5,22,30-33} Unlike the premature contractions of adult life which tend to disappear on increase of the heart rate following exercise, the fetal premature contractions have been found to occur with increased frequency during the tachycardia accompanying the fetal startle reflex.²² These fetal premature contractions are of little clinical significance, and were found to disappear a few days after birth.²⁷

A third type of arrhythmia described by Hyman²⁷ is a gross irregularity of the fetal heart, which when pronounced suggested auricular fibrillation. It occurred in eleven cases associated with sudden interruption of pregnancy or difficulty in resuscitation of the infant after delivery.

Fenichel and Kurzrok³⁴ described blocked auricular extrasystoles in a fetus, which persisted after birth and were confirmed by postnatal electrocardiograms. Geiger and Hines³⁵ discussed the prenatal diagnosis of complete and partial congenital heart block. Plant and Steven⁴⁵ reported a case of complete A-V block in which the fetal electrocardiogram showed a rate of 56 per minute. The postnatal electrocardiogram showed complete A-V dissociation with an auricular rate of 114 and a ventricular rate of 50 per minute.

Factors Influencing the Success of Fetal Recordings.—The earliest recordings of the fetal electrocardiogram have been obtained in the sixteenth week of preg-

nancy^{2,5,6,9} in a small percentage of attempts. Bernstein and Mann⁵ found in their series of 153 records a sharp drop in the percentage of positive cases recorded in the seventh and eighth lunar months as compared with the preceding and subsequent months. Goodyer⁶ in a series of 181 records was unable to show any significant drop in the incidence of positive tracings over that period. However, the data of these authors show a very definite decrease in the average amplitude of the fetal deflection during those two months. On compiling all the published cases amenable to analysis by lunar months of pregnancy, including the large series of Goodyer, this drop in the incidence of positive tracings can be demonstrated as shown in Table I. Out of the composite group of 482 tracings, 90 per cent of those taken in the sixth month and 92 per cent of those in the ninth month were positive, while in the seventh and eighth months only 75 per cent and 65 per cent, respectively, were positive. Application of the formula for the

standard error of the difference between two proportions,³⁶
$$\sqrt{\frac{p_1 \times q_1}{n_1} + \frac{p_2 \times q_2}{n_2}}$$

shows that both the fall in positive results from the sixth to the seventh month, and the rise from the eighth to the ninth month are significant at the level of significance where the possibilities are five out of 100 that the difference might be due to chance.

The reason for this fall in the incidence of positive results is not apparent. It has been pointed out⁶ that early in pregnancy the small size of the fetus compared with the relatively large amount of amniotic fluid and lack of contact between uterus and abdominal wall might account for the inability to pick up the fetal potentials. These factors do not account for the fall in positive results occurring later in pregnancy. It has been suggested^{5,37} that a sudden relative increase in the amount of amniotic fluid with regard to the fetal mass during the seventh and eighth months could explain the drop in positive tracings. There is no support for this view in the available data on the volume of amniotic fluid. The amount of fluid increases progressively until the seventh month, after which it decreases in amount until term.³⁸ Furthermore, even hydramnios has not prevented the recording of the fetal electrocardiogram.^{6,39}

Other factors that are believed to reduce the chances of obtaining positive tracings are the thickness of the abdominal wall and the interposition of the placenta. While it has been shown that fetal deflections obtained directly from the uterus are much larger than those recorded from the abdomen,¹⁷ and while many workers have felt that obesity reduces the chances of recording fetal potentials, Goodyer and associates⁶ could find no correlation between the height-weight ratio, an index of bodily habitus, and the incidence of positive results. In the current series, very little difference was found between the height-weight ratio of women yielding positive and negative tracings.

The size of the fetus is thought by some to be related to the incidence of positive tracings. Bell⁴ could not confirm this and Goodyer⁶ was unable to show a correlation between the fetal wave amplitude at term and the birth weights in the same cases.

Apparently there are more decisive factors than thickness of the abdominal wall, amount of amniotic fluid, or weight of the fetus in influencing the incidence of positive tracings. Borter³⁹ suggests individual variations in tissue conductivity as the most important factor. However, it has been noted in this series as well as in those of others that the same cases in which tracings are negative on one occasion may show fetal waves of good amplitude a week or two later. The main factors governing the ability to record the fetal electrocardiogram have yet to be determined.

Factors that interfere with the recognition of recorded fetal waves include excessive somatic tremor, poor electrical contact, amplifier noise, and outside electrical interference. Fetal and uterine movements also produce electrical potentials.^{40,41} All of these cause disturbances in the baseline of the tracing and tend to hide small fetal deflections. If there is marked fetal sinus arrhythmia, small deflections that might otherwise be recognized by their regular recurrence amidst the irregularly spaced baseline artifacts can no longer be identified, and such tracings would appear negative.

Clinical Applications of the Method.—While many applications of fetal electrocardiography have been suggested by those intrigued with the technique, in most cases other methods of obtaining the same information are available, which are simpler in performance and more reliable in their results. The rarity of the occasions in which fetal electrocardiography alone is indicated accounts for the lack of interest on the part of obstetricians in this technique.

1. *Diagnosis of Pregnancy:* Bell⁴ pointed out that the recording of fetal potentials constitutes a test which unlike the biologic tests does not give false results. However, the biologic tests become positive within a two- to three-weeks' period after conception,³⁸ while fetal electrocardiograms do not become positive until the sixteenth week. It is only in cases where the biologic tests are positive yet pregnancy doubted, such as in hydatidiform mole or chorionepithelioma, that fetal electrocardiography might be used to aid in diagnosis. In pseudocyesis, or amenorrhea with abdominal tumors, a negative electrocardiogram would only supplement a negative biologic test.

2. *Diagnosis of Multiple Pregnancy:* Theoretically, multiple pregnancies may be diagnosed a few weeks sooner by electrocardiography than by any other method. X-ray examination does not become positive until the fifth month.⁴² There have been six cases reported in the literature of the electrocardiographic diagnosis of multiple pregnancies. However, there have been reports of four cases of twins in which only a single fetal heart was detected, a case of triplets in which only two fetal hearts were detected, and a case of twins with hydramnios in which no fetal deflections were found. This record of about 50 per cent accuracy of diagnosis is not at all impressive compared with the reliability of x-ray diagnosis.

3. *Diagnosis of Fetal Position:* As pointed out earlier, upward deflections or the initial upward deflections of diphasic waves may not always signify breech presentations. Where the initial upward deflection is small compared with the

succeeding downward deflection, and the baseline irregular, the diagnosis of a breech may be missed. In Fig. 2, taken from a case of twins, shown by x-ray study to be vertex and breech, both sets of deflections are predominantly downward. On careful examination, however, a smaller and inconstant upward deflection preceding the larger downward component is found in one of the sets of potentials; that of the breech. Since anomalies of the cardiac morphology, physiology, and of the position of the heart in the fetal chest affect the electrical axis, the diagnosis of fetal position by electrocardiography is unreliable.

4. *Diagnosis of Fetal Arrhythmias:* Careful auscultation may reveal fetal arrhythmias, and they can be recorded for more careful study by the stethograph as well as by the electrocardiograph. The absence of P waves in the record deprives the electrocardiogram of its theoretical advantage in the diagnosis of arrhythmias. However, where funic or uterine souffle or other auditory interference prevents recording of the heart sounds, the heart potentials may still be obtained. Furthermore, use of the paper writing electroencephalograph apparatus will give long records at a minimum of expense.

5. *Diagnosis of Congenital Anomalies:* It has been suggested that the prenatal diagnosis of congenital cardiac anomalies might be made by the discovery of prolongation of the fetal QRS time due to the slowing of conduction around a defect in the ventricular septum. No such diagnoses have as yet been made. In one case of extensive cardiac malformation, including absence of the inter-ventricular septum, the prenatal electrocardiogram was found to be normal.⁹ In a case of the absence or imperfect development of the bundle of His with complete A-V dissociation, the fetal deflections were not prolonged.⁴⁵ On the other hand, diagnoses of congenital defects have been made by discovery of fetal murmurs, sometimes in conjunction with fetal arrhythmias.^{30,32,43,44} Fetal stethography lends itself well to the accurate study of this type of case, since murmurs as well as the fetal rhythm are recorded, and is therefore to be preferred over electrocardiography in the prenatal diagnosis of congenital heart disease.

6. *Diagnosis of Fetal Life:* The unique value of the electrocardiograph in obstetrical practice is in the determination of fetal life in those rare cases in which fetal sounds and movement cannot be detected. The biologic tests continue to be positive for weeks after the death of the fetus, but the finding of fetal deflections is convincing proof of a living fetus. At term the incidence of positive results is between 90 and 100 per cent, depending on the technique used. Furthermore, the technique is simple and the results immediately available. Although fetal electrocardiography has not fulfilled much of its early promise, in this particular obstetrical problem it is the only method that can be relied upon to yield the necessary information.

CONCLUSIONS

1. The technique of fetal electrocardiography is both simple and practical, as shown by a suggested standard technique.

2. The use of the electroencephalograph is to be preferred to the use of specially constructed or modified electrocardiographs, since the former is available in many large hospitals, is more sensitive, and yields better results.

3. At or near term, the standard electrocardiograph adjusted to double standardization may also be used satisfactorily to record the fetal electrocardiogram.

4. The main practical application of fetal electrocardiography in obstetrics is in the diagnosis of fetal life where fetal heart sounds and movements are absent. In these cases, the procedure is rapid and reliable, with no false positive results.

I am indebted to Dr. Charles E. Kossmann for suggestions in the preparation of this report, and to Mrs. Marion Shares and Miss Elaine Kaplan for valuable technical assistance.

REFERENCES

1. Strassmann, E. O.: Technic and Results of Routine Fetal Electrocardiography During Pregnancy, *Proc. Staff Meet., Mayo Clin.* 13: 251, 1938.
2. Ward, J. W., and Kennedy, J. A.: Recording of the Fetal Electrocardiogram, *AM. HEART J.* 23: 64, 1942.
3. Maekawa, M., and Toyoshima, J.: Fetal Electrocardiograms of the Human Subject, *Acta scholae med. univ. imp. in Kioto* 12: 519, 1930.
4. Bell, G. H.: Human Foetal Electrocardiogram, *J. Obst. & Gynaec. Brit. Emp.* 45: 802, 1938.
5. Bernstein, P., and Mann, H.: A Clinical Evaluation of Fetal Electrocardiography, *Am. J. Obst. & Gynec.* 43: 21, 1942.
6. Goodyer, A. V. N., Geiger, A. J., and Monroe, W. M.: Clinical Fetal Electrocardiography, *Yale J. Biol. & Med.* 15: 1, 1942.
7. Lindsley, D. B.: Heart and Brain Potentials of Human Fetuses in Utero, *Am. J. Psychol.* 55: 412, 1942.
8. Dressler, M., and Moskowitz, S. N.: Fetal Electrocardiography and Stethography, *Am. J. Obst. & Gynec.* 41: 775, 1941.
9. Mann, H., and Bernstein, P.: Fetal Electrocardiography, *AM. HEART J.* 22: 390, 1941.
10. Strassmann, E. O.: Development of Fetal Electrocardiography, *Tri-State M. J.* 15: 2880, 1943.
11. Cremer, M.: Ueber die direkte Ableitung der Aktionsströme des menschlichen Herzens vom Oesophagus und über das Elektrokardiogramm des Fötus, *München. med. Wchnschr.* 53: 811, 1906.
12. Foa, C.: L'elettrocardiogramma Fetale, *Arch. ital. de biol.* 56:145, 1911 (Quoted by Goodyer⁶).
13. Krumbhaar, E. B.: Electrocardiographic Studies in Normal Infants, *Am. J. Physiol.* 40: 133, 1916.
14. Easby, M. H.: Electrocardiograms From a Four and a Half Months Old Fetus, *AM. HEART J.* 10: 118, 1934.
15. Heard, J. D., Burkley, G. G., and Schaefer, C. R.: Electrocardiograms Derived from Eleven Fetuses Through Medium of Direct Leads, *AM. HEART J.* 11: 41, 1936.
16. Marcel, M. P., and Exchaquet, J. P.: L'elettrocardiogramme du foetus humain avec un cas de double rythme auriculaire 'verifié, *Arch. d. mal. du coeur* 31: 504, 1938.
17. Mann, H., and Mayer, M. D.: The Uterine Electrocardiogram, *J. Mt. Sinai Hosp.* 8: 805, 1942.
18. Putz, T., and Ullrich, O.: Fortschritte auf dem Gebiet der fetalen Elektrokardiogrammfor-schung, *Arch. f. Gynäk.* 171: 199, 1941.
19. Strassmann, E. O., and Mussey, R. D.: Technic and Results of Routine Fetal Electrocardiography During Pregnancy, *Am. J. Obst. & Gynec.* 36: 986, 1938.
20. De Lee, J. B., and Greenhill, J. P.: *The Principles and Practice of Obstetrics*, ed. 8, Philadelphia, 1943, W. B. Saunders Co.
21. Chalier, J., and Froment, R.: Fièvre typhoïde avec oscillations thermiques . . . : correlations numériques entre les bruits du coeur du foetus et de la mère, *Lyon Méd.* 154: 361, 1934.
22. Sontag, L. W., and Newberry, H.: Incidence and Nature of Fetal Arrhythmias, *Am. J. Dis. Child.* 62: 991, 1941.
23. Sontag, L. W., and Wallace, R. F.: The Effect of Cigaret Smoking During Pregnancy Upon the Fetal Heart Rate, *Am. J. Obst. & Gynec.* 29: 77, 1935.

24. Rech, W.: Untersuchungen über die Herztätigkeit des Fetus, *Arch. f. Gynäk.* 147:82, 1931.
25. Sontag, L. W., and Richards, T. W.: Studies in Fetal Behavior: I. Fetal Heart Rate as a Behavioral Indicator, *Monog. Soc. Res. Child Devel.* vol. 3, no. 4, 1938.
26. Sontag, L. W., and Newberry, H.: Normal Variations of Fetal Heart Rate During Pregnancy, *Am. J. Obst. & Gynec.* 40: 449, 1940.
27. Hyman, A. S.: Irregularities of the Fetal Heart, *Am. J. Obst. & Gynec.* 20: 332, 1930.
28. Davis, M. E., and Potter, E. L.: Intrauterine Respiration of the Human Fetus, *J.A.M.A.* 131: 1194, 1946.
29. Windle, W. F.: *Physiology of the Fetus*, Philadelphia, 1940, W. B. Saunders Co.
30. Dippel, A. L.: Two Cases of Congenital Heart Disease in Which the Diagnosis was Made Before Birth, *Am. J. Obst. & Gynec.* 27: 120, 1934.
31. Burnham, L.: Unusual Irregularity of the Fetal Heart During Pregnancy, *Am. J. Obst. & Gynec.* 37: 164, 1939.
32. Roberts, J. T.: Diagnosis of Congenital Heart Disease Before Birth and the Hereditary Factor in Congenital Heart Disease, *J. Tech. Methods* 18: 101, 1938.
33. Barré, J. A., and Henriot, P.: Un cas d'arythmie extra-systolique foetale, *Bull. Soc. d'obst. et de gynéc.* 24: 74, 1935.
34. Fenichel, N. M., and Kurzrok, L.: Congenital Heart Disease Manifesting Arrhythmia in Utero, *New York State J. Med.* 42: 151, 1942.
35. Geiger, C. J., and Hines, L. E.: Prenatal Diagnosis of Complete Congenital Heart Block, *J.A.M.A.* 115: 2272, 1940.
36. Hill, A. B.: *Principles of Medical Statistics*, ed. 3, London, 1942, Lancet, Ltd.
37. Paley, S. S., and Krell, S.: Fetal Electrocardiography and Stethography, *Am. J. Obst. & Gynec.* 48: 489, 1944.
38. Beck, A. C.: *Obstetrical Practice*, ed. 3, Baltimore, 1942, Williams & Wilkins Co.
39. Borter, W.: Beitrag zur Frage der fötalen Elektrokardiographie, *Monatschr. f. Geburtsh. u. Gynäk.* 116: 9, 1943.
40. Strassmann, E. O.: The Fetal Electrocardiogram Late in Pregnancy, *Proc. Staff Meet., Mayo Clin.* 11: 778, 1936.
41. Frade, M. and Bedoya, J. M.: Técnica y Resultados de Electrocardiografía Fetal Intrauterina, *Medicina, Madrid* 13: 74, 1945.
42. Santé, L. R.: *Principles of Roentgenological Interpretation*, ed. 4, Ann Arbor, Mich., 1942, Edwards Bros., Inc.
43. Sampson, J. J., McCalla, R. L., and Kerr, W. J.: Phonocardiography of the Human Fetus, *AM. HEART J.* 1: 717, 1926.
44. Smith, A. L.: Recording and Reproduction of a Fetal Heart Murmur Confirmed After Birth, *Arch. Pediat.* 58: 549, 1941.
45. Plant, R. K., and Steven, R. A.: Complete A-V Block in a Fetus, *AM. HEART J.* 30:615, 1944.

CIRCULATORY ADAPTATIONS IN AYERZA'S SYNDROME—BLACK CARDIACS

ALBERTO C. TAQUINI, M.D.,* J. C. FASCILOLO, M.D.,
J. R. E. SUAREZ, M.D., AND H. CHIODI, M.D.
BUENOS AIRES, ARGENTINA

CLINICAL and anatomic studies have led to the conclusion that Ayerza's disease is only a form of *chronic cor pulmonale with cyanosis*. It would seem now that the sclerosis of the pulmonary artery that was considered very important before is actually only secondary to the chronic bronchopulmonary ailments that determine the disease.

From a functional standpoint these pulmonary ailments lead to alveolar hypoventilation, which is the first link of a chain in the physiopathologic picture of these patients. Alveolar hypoventilation produces anoxemia with varying degrees of arterial unsaturation and also increase of the carbon dioxide tension in the blood. Arterial unsaturation leads to the increase of the erythropoietic activity of the bone marrow, thus originating hyperglobulia and an increase of hemoglobin, which added to the arterial unsaturation, determines the marked cyanosis which characterizes these patients. Thus is explained, on a physiopathologic basis, the clinical picture shown by patients who have been referred to as black cardiacs.^{2-4,5,15}

Even though these studies have permitted the explanation of the physiopathogenesis of this syndrome, there exist certain facts, concerning which there are still some doubts. For example, it has not yet been explained why, if the alveolar hypoventilation is the only cause of anoxemia, the oxygen tension in the arterial blood of these patients is usually markedly lower than the alveolar oxygen tension. Neither do we know why some patients, in spite of having marked alveolar hypoventilation, never have the clinical features shown by black cardiacs.

Both these facts have induced some authors to support the theory that the clinical features of the black cardiacs only appear when the oxygenation of the blood is impeded by a disorder in the oxygen diffusion in the lungs; this disorder might be related to the much-discussed primary sclerosis of the pulmonary artery.

On the other hand, patients with Ayerza's disease present to the physician the problem of circulatory and respiratory adaptation, not thoroughly studied yet, that permits them to withstand such unfavorable conditions for so many years.

Read at the Inter-American Congress of Cardiology, Mexico, D. F., Oct. 5-12, 1946.

*From the Facultad de Ciencias Médicas de Buenos Aires, Centro de Investigaciones Cardiológicas, Fundación Virginio F. Grego.

In order to clarify these facts, we have accomplished a study on the circulatory and respiratory functions of a group of patients of this type in different periods of the evolution of the disease.

This study was made on sixteen patients with varying degrees of pulmonary fibrosis and emphysema.

A cough of long duration and repeated bronchitis were registered in the history of all patients. Eight had also suffered asthmatic attacks. All the patients presented effort dyspnea. Fourteen had marked cyanosis, and nine presented all the clinical features characteristic of Ayerza's syndrome.

In Table I the main characteristics of each patient are shown. As can be seen, eight of the patients were suffering from cardiac insufficiency when they came under our care. The diagnosis in these patients was reached through the following findings: cardiac enlargement, gallop rhythm, tricuspid murmur, hepatic congestion, and increased venous pressure. Dyspnea was considered as a symptom of cardiac failure only when it appeared during rest and in the absence of bronchial spasm. Edema, so often found in these patients, was considered as a sign of cardiac failure only when it was marked and accompanied by hepatic congestion and increased venous pressure.

DETERMINATIONS MADE AND METHODS EMPLOYED

In the analysis of the patients a study was made of the respiratory, circulatory, and blood functions, according to techniques stated and in the following order:

Lung volume and its subdivisions were determined by Christie's method,⁷ modified by Robinson.²³

Alveolar air was collected with a test tube of 20 mm. diameter and 100 c.c. capacity, with a Müller valve in one end and a three-way stopcock in the other. In patients in whom it was not possible to obtain air instantaneously, the sample was taken four seconds afterward (expulsion, more than 600 cubic centimeters).

Serial alveolar air was determined by taking samples after the exhalation of 500, 900, and 1,300 c.c. within six seconds.

Lung ventilation was determined in a gasometer of 600 liters in twenty-minute periods with measurements every minute. All volumes are expressed at 37°C., prevailing barometric pressure, and complete saturation with water vapor.

Cardiac output was determined by Grollman's¹² four-sample method.

Blood volume was determined by the Gibson and Evans¹¹ technique with Evelyn's photocolorimeter.

Venous pressure was determined by the direct method: Lyons, Kennedy, and Burwell²⁰ technique.

Circulation time: Decholin and ether were used for the arm-to-tongue and arm-to-lung circulation times, respectively.

Arterial blood examinations were made of the arterial blood withdrawn from the femoral artery and heparinized, using the Van Slyke apparatus.

Calculation was made of the carbon dioxide tension and the pH of arterial blood by the nomogram and Cartesian chart of Henderson and associates¹³ and by Henderson and Hasselbach's equation. *Free carbon dioxide in serum* was calculated with the solubility coefficient of Van Slyke and co-workers²⁹; $pK = 6.11$, according to Dill, Daly, and Forbes.¹⁰

TABLE I. MAIN CLINICAL CHARACTERISTICS OF PATIENTS STUDIED

CASE	AGE	SEX	PULMONARY				HEART				ARTERIAL PRESSURE	DYSPNEA	CYANOSIS	EDEMA	RED CELLS
			EMPHY- SEMA	FIBROSIS	ASTHMA	SCLEROSIS OF PUL- MONARY BRANCHES	ENLARGE- MENT OF HEART	DILATA- TION OF PUL- MONARY TRUNK	DEVIATION OF ELEC- TRICAL AXIS TOWARD RIGHT	RIGHT HEART INSUFFI- CIENCY					
1 (E. A.)	60	M	+	+++	+	+++	++	+	-	-	160/80	+++	++	++	6,400,000
2 (P. C.)	46	M	+	+	+	+	+	+	+	-	130/90	++	+	-	5,800,000
3 (V. F.)	53	M	+	+	+	+	+	++	-	+	180/120	+++	++	+	6,300,000
4 (D. Fl.)	40	M	++	++	++	++	+	++	+	-	170/105	++	+++	+	7,300,000
5 (M. R.)	49	M	+++	++	+	++	-	+++	-	-	150/105	++	+	-	5,600,000
6 (F. T.)	55	M	++	+++	++	++	++	+	-	-	140/85	++	+	-	4,500,000
7 (R. A.)	35	M	++	+	+++	++	+	++	+	+	170/110	++	++	++	6,700,000
8 (J. M.)	52	M	+	++	++	++	+	++	-	-	135/110	++	++	-	6,900,000
9 (A. T.)	58	M	++	++	++	++	+	+	+	-	125/80	+++	++	-	5,600,000
10 (M. A.)	64	M	++	++	+	++	++	++	+	++	170/110	++	+++	++	7,690,000
11 (F. B.)		M	++	+++	+	++	++	+	+	+	125/70	++	++	+	6,400,000
12 (M. B.)		M	+++	+++	+	+++	++	++	+	++	135/85	++	+++	++	6,410,000
13 (D. Fe.)	51	M	+	+	++	+	++	+	+	++	155/110	++	+++	++	7,500,000
14 (L. G.)	62	M	+	++	+	++	++	++	-	++	180/120	++	++	+++	6,900,000
15 (G. S.)	54	M	++	+++	+	++	++	++	+	+++	120/80	+++	+++	++	7,400,000
16 (N. S.)		M	++	++	++	++	+	++	-	-	220/115	++	+	-	4,700,000

+, light; ++, moderate; +++, marked; +++++, severe.

Oxygen tension in the arterial blood was calculated by interpolation in the dissociation curve, which was constructed with points to 20, 30, and 60 mm. Hg of oxygen and 40 mm. Hg of carbon dioxide, to pH 7.40. A standard curve was used in those patients in whom a dissociation curve was not constructed.

RESPIRATORY FUNCTION

Lung Volume and Its Subdivisions.—The study made of the pulmonary function demonstrated the characteristic picture of emphysema with pulmonary fibrosis (Fig. 1). In all the patients there was observed a real or relative increase

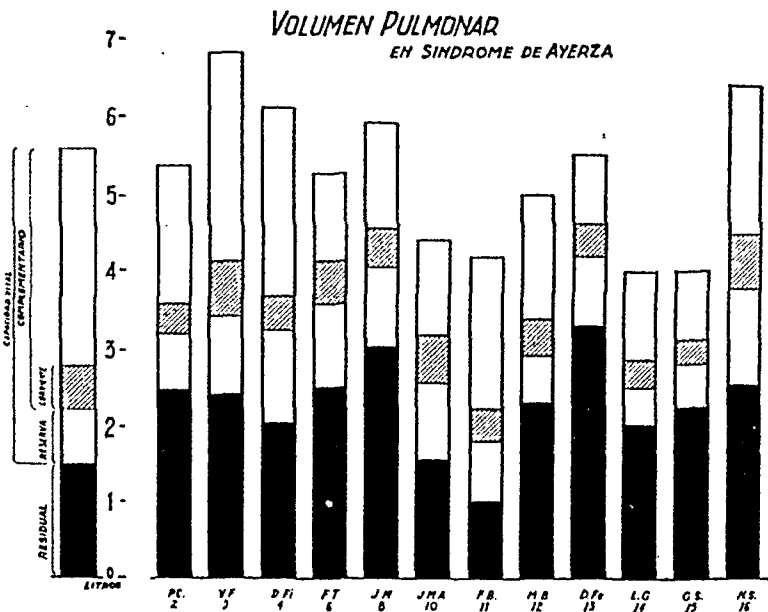


Fig. 1.—Pulmonary volume in patients with Ayerza's syndrome. The first column represents the mean normal values found in persons of more or less the same age. The following columns represent the values found in each individual case studied.

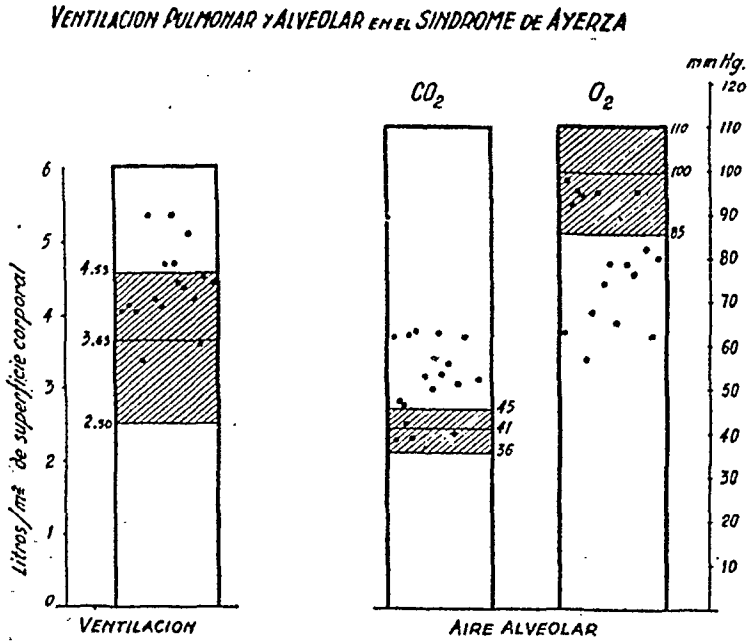


Fig. 2.—Pulmonary and alveolar ventilation. The points in each column represent the individual values found in the patients studied. The striped zone indicates the normal limits found in persons of more or less the same age. The central line represents the mean normal value.

of the residual air. Residual air values varied between 1 and 3.18 liters with a mean value of 2.27, which are above the normal figures. On the contrary, the reserve air, as well as the tidal air and the complementary air, was found diminished in most of the patients, the figures varying between 0.50 and 1.26 liters for the reserve air, 0.30 and 0.70 liter for the tidal air, and 0.90 and 2.77 liters for the complementary air. The modifications registered showed a marked increase in the relationship between the residual air and the total lung capacity in all patients except one.

Lung Ventilation.—In the patients studied there was an increase of the lung ventilation, the figures oscillating between 3.33 and 5.68 liters per minute and per square meter of body surface (Fig. 2). This increase was a consequence of the respiratory frequency, because, as we have already said, the tidal air was diminished in most of the patients.

Alveolar Air.—The study made of the alveolar air showed in most of the patients a marked diminution of the oxygen tension and an increase of the carbon dioxide tension. The highest and lowest figures for oxygen were 98.5 and 57.0 mm. Hg, respectively, and for carbon dioxide, 63.9 and 38.2 mm. Hg; the mean values were 85 for the first and 51.8 for the latter (Fig. 2). These quantities demonstrate that in most of these patients there existed a rather important diminution of the alveolar ventilation in spite of their increased lung ventilation.

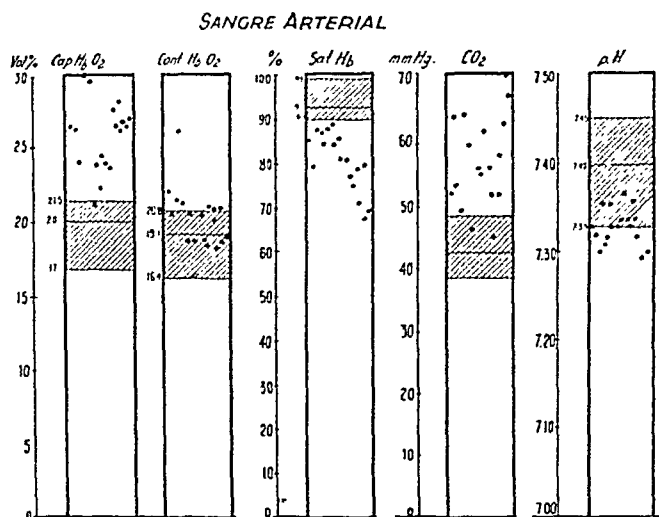


Fig. 3.—Hemoglobin, oxygen, carbon dioxide, and pH of the arterial blood. The points in each column represent the individual values found in the patients studied. The striped zone and the horizontal line drawn through the same represent the normal limits found in persons of more or less the same age and the mean normal value.

Arterial Blood (Fig. 3).—The study of the arterial blood of these patients showed an increase in the oxygen capacity that oscillated between 21.35 and 30 volumes per cent, as was to be expected from the polyglobulia and increase of hemoglobin mentioned before.

Oxygen and carbon dioxide tensions of the arterial blood showed figures ranging between 36 and 57.5 mm. Hg for the first tension and 46 and 67.2 for the second.

Together with the decrease of the oxygen tension in arterial blood a rather important degree of arterial unsaturation was found, hemoglobin figures in different patients being between 66.4 and 87.5 per cent. Although, as the blood's hemoglobin content was increased in most of the patients, the quantity of oxygen contained in arterial blood was slightly increased, the figures ranging between 17.86 and 22.24 per cent.

On the other hand, the carbon dioxide increases. Although almost compensated for by the increase of bicarbonate, pH of arterial blood showed in most of the patients a change to acidity, the figures found oscillating between 7.29 and 7.39, with a mean value of 7.33.

Discussion.—The group of patients studied from the respiratory standpoint showed (1) diminution of the respiratory efficiency, (2) alveolar hypoventilation, (3) increase of the oxygen capacity of the blood, and (4) marked unsaturation of the arterial blood with an increase of the carbon dioxide tension and a decrease of the pH.

The comparison of the oxygen tension both in the alveoli and in the arterial blood revealed a marked difference in our patients (Fig. 4). This difference, which has been observed by most investigators of the subject, is, as has been said, one of the reasons against the hypothesis that points to alveolar hypoventilation as the only cause for anoxemia.

There are at least three mechanisms which can explain the difference in the alveolar and arterial oxygen tension: (1) the existence of a disorder of diffusion that impedes the free passing of the oxygen through the alveolar wall to the blood;

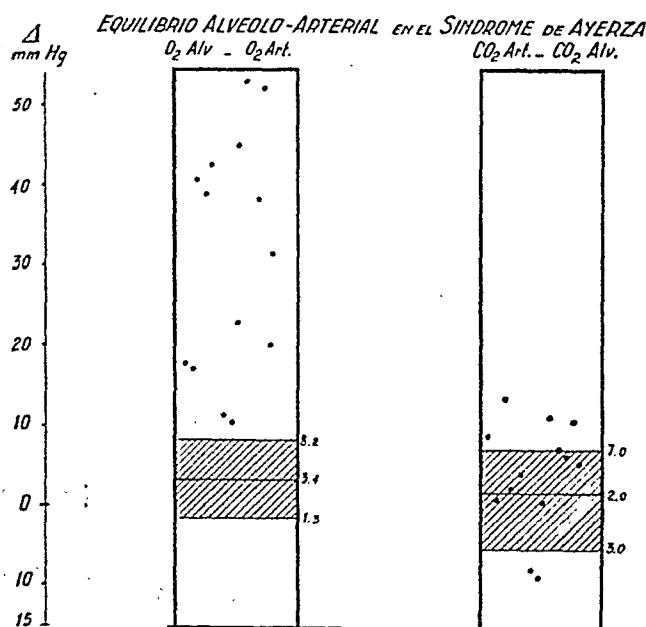


Fig. 4.—Alveolar-arterial equilibrium found in Ayerza's syndrome. Each point represents the equilibrium found in each individual case. The striped zone represents the normal limits found in normal persons of more or less the same age.

(2) the existence of arteriovenous shunts in the lung that permits some of the venous blood to pass through the lung without being converted into arterial blood; or (3) the irregular distribution of gases in the lungs which determines the existence of zones with different oxygen tensions.

As most of these patients had an increase of residual air and a diminished respiratory efficiency, it was thought at first that there was an irregular distribution of the gases in the lungs, a fact which has been proved in patients with emphysema.^{5,7b,9,14,24,25,27,30} If this is what happens, the alveolar air, determined according to Haldane and Priestley's technique, would be the resultant of the combination of gases from different zones of the lung; each gas content would have a different composition and, therefore, the arterial blood would not be necessarily in equilibrium with alveolar oxygen (due to the presence of hemoglobin and the shape of its oxygen dissociation curve).

In order to study this problem three serial alveolar samples were taken, one after another, in the first six seconds of a deep expiration, the first one at 500 c.c., and the third one at 1,300 c.c., in those patients in whom expiration was large and rapid. In those patients in whom slow expiration prevented to obtain the aforementioned quantities within a period of six seconds, two samples were taken: one at 500 c.c., and the second, at the end of the mentioned period of time. Analysis was made of the samples thus obtained, and there were found to be noticeable differences in their composition in most of the patients (Table II).

The existence of this irregular distribution of the gas in the lung explains the increase in the difference between alveolar and blood O_2 tensions in most of the patients studied. This leads us to point out hypoventilation and uneven gas distribution as the causes of anoxemia in these persons. Notwithstanding, one patient (Case 10) showed normal oxygen and carbon dioxide tensions: 91 and 97 mm. Hg were the figures found for the oxygen tension and 40.8 and 38.2 mm. Hg for the carbon dioxide in duplicate determinations. Moreover, the serial alveolar air did not show significant abnormalities. From these facts we might conclude that in this patient there existed a satisfactory alveolar ventilation. Nevertheless, the arterial blood of this patient showed a high grade of anoxemia, since the oxygen tensions in the blood were only up to 45.2 and 43.5 in the two samples simultaneously analyzed, and so the alveolar-arterial oxygen difference is 45.8 and 53.5 mm. Hg, respectively. If it is true that even in this case it is possible to think that there existed certain deep zones of the lung in which the air was so inadequately renewed that those zones could not be reflected in the samples of alveolar air, we have also to take into consideration the probable existence of either a diffusion disorder irregularly distributed in the alveoli or arteriovenous shunts in the lung. These last hypotheses might be supported in this case by the facts that the patient (Case 10) had had a brief pulmonary clinical history; that the residual air was slightly augmented; and that post-mortem examination revealed predominately lesions of the arterioles and capillaries of the lung.

In summary it can be said that the studies made show that most patients with the Ayerza syndrome did not have a regular distribution of gases in the

lungs. The anoxemia that they presented on this basis is explained, although we will have also to consider as probable, in certain cases, the existence of a diffusion disturbance irregularly distributed or arteriovenous shunts as a consequence of chronic ailments of the lung.

TABLE II. SERIAL ALVEOLAR AIR TAKEN IN NORMAL PERSONS AND IN PATIENTS WITH AYERZA'S SYNDROME (DIFFERENCES IN TENSIONS OF OXYGEN AND CARBON DIOXIDE, FOUND IN SAMPLES TAKEN AT DIFFERENT TIMES DURING EXPIRATION, ARE FOUND TO BE MORE MARKED IN THE PATIENTS STUDIED THAN IN NORMAL PERSONS)

AYERZA'S SYNDROME						
CASE	CO ₂ % ALVEOLAR			O ₂ % ALVEOLAR		
	SAMPLE 1	LAST SAMPLE	DIFFERENCE	SAMPLE 1	LAST SAMPLE	DIFFERENCE
D. F. 4	6.29	6.80	.51	12.68	11.49	1.19
	5.93	6.78	.85	13.69	11.46	2.23
M. J. R. 5	5.91	6.68	.97	14.33	12.60	1.73
R. A. 7	6.37	8.80	2.43	12.13	7.58	4.55
D. Fe. 13	6.20	6.97	.77	12.80	11.43	1.37
	6.47	6.63	.16	12.54	11.37	1.17
C. S. 15	8.16	8.72	.56	11.38	9.97	1.41
Average			.99			2.13

NORMAL SUBJECTS

SUBJECT	CO ₂ % ALVEOLAR			O ₂ % ALVEOLAR		
	SAMPLE 1	LAST SAMPLE	DIFFERENCE	SAMPLE 1	LAST SAMPLE	DIFFERENCE
M. V	5.69	6.20	.51	14.00	13.69	.31
	6.17	6.41	.24	14.82	14.07	.75
L. C. F.	4.55	5.05	.50	16.34	15.61	.73
	4.42	4.44	.02	16.89	16.84	.05
J. R. S.	5.86	6.25	.39	12.31	11.16	1.15
	5.65	5.87	.22	13.11	13.11	0.00
M. Ch.	5.68	5.84	.16	13.30	12.58	.72
	5.52	5.80	.28	14.19	13.78	.41
A. M.	3.46	3.86	.40	17.08	16.25	.83
	3.63	3.94	.31	16.74	16.00	.74
Average			.30			.57

The presence or absence of cyanosis and the degree of the same in these patients can be explained by the degree of oxygen unsaturation as well as the increase in hemoglobin observed in almost all of them (Fig. 5).

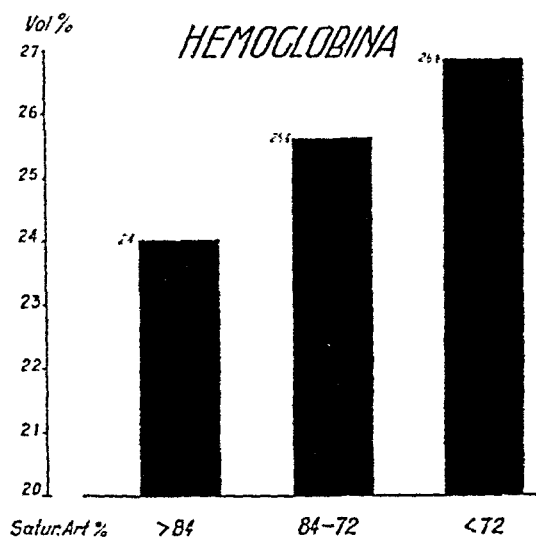


Fig. 5.—Hemoglobin amount in relation to anoxemia. Each column represents the average value of hemoglobin (in volume per cent) in each of the groups in which the patients were classified according to the degree of arterial saturation.

CIRCULATORY FUNCTION

Blood Volume.—In the ten patients studied, the total blood volume oscillated between 5.21 and 11.95 liters; these quantities corresponded to 72.4 to 163.7 c.c. per kilogram of body weight (Fig. 6). These figures coincided with normal standards in only two of the ten patients studied; they were markedly higher than normal in the remaining eight. The increase in the blood volume varied from 12 to 121 per cent. Since some of our patients presented cardiac failure, with noticeable edema, the figure of volume per meter of height was taken as a comparative index, in relation to our standards. When these calculations were made, all the patients studied showed an increase of the blood volume, which varied from 13.5 to 142 per cent, with an average increase in the ten patients of 55.3 per cent. The plasma volume varied from 2.28 to 3.08 liters, which corresponded to 32.5 and 53.1 c.c. per kilogram of body weight. In three patients the plasma volume was found to be within normal limits, in five there was a moderate diminution, and in two a moderate increase was observed; the whole group deviation was +3.98 per cent.

The erythrocyte volume varied between 2.93 and 9.02 liters, which corresponded to 36.9 and 125.5 c.c. per kilogram of body weight. In all the patients there was an increase of the erythrocyte volume that varied from 9 to 241.1 per cent.

These results show that in our patients with Ayerza's disease there exists an increase of the blood volume due to an increase of the red cells. The plasma volume, on the contrary, was found to be practically normal because the varia-

VOLUMEN SANGUINEO SINDROME de AYERZA

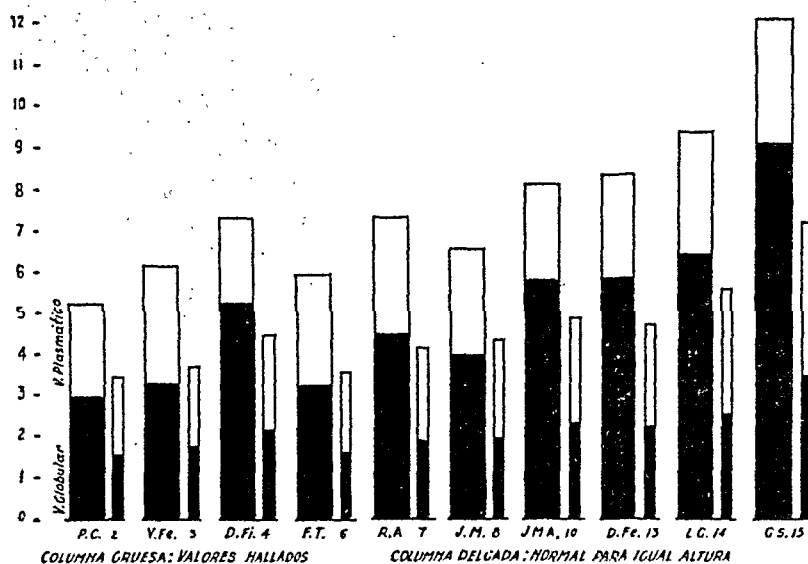


Fig. 6.—Blood volume found in Ayerza patients. The thick columns represent the figures found in the different cases. The thin columns represent the normal values of persons of similar heights.

VOLUMEN SANG. - VALORES MEDIOS

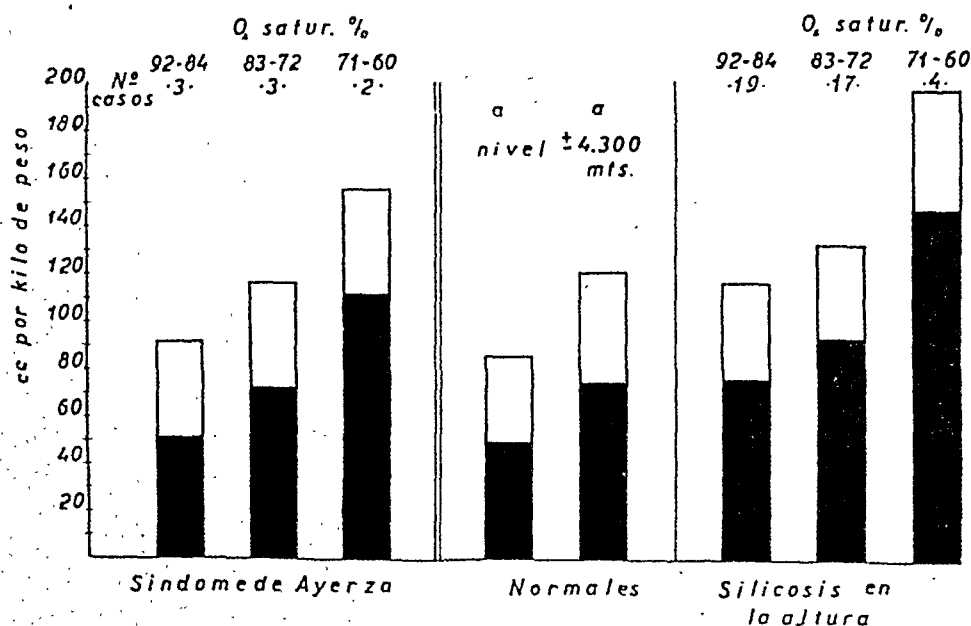


Fig. 7.—Average blood volume found in each group of patients with Ayerza's syndrome, with different degrees of arterial saturation, compared with the values found by Hurtado and associates in normal persons and in patients with silicosis.

tions registered were very small and the existence of edema as well as the undernourishment of some patients made possible the presence of errors in the calculation of the plasma volume per kilogram of body weight. Since the most marked increases of the blood volume coincided with the lowest figures of oxygen saturation in the blood, it is logical to accept the fact that the increase of the erythrocyte volume is provoked by the stimulation of the bone marrow by anoxemia.

The existence of a relation between both factors was clearly shown when the patients were divided into three groups with blood saturations between 84 and 92 per cent for the first group, 72 and 84 per cent for the second, and 61 and 72 per cent for the third group (Fig. 7). The individual variations registered can be explained by factors such as sex, the patient's condition, intercurrent infections, and recent variations in the oxygenation of the blood. Nevertheless, it must be admitted that there are personal variations, because even normal persons give different marrow responses to different grades of anoxemia, as has been pointed out by Hurtado, Merino, and Delgado.¹⁶

Since the highest blood volumes were found in patients suffering from cardiac failure, it might be possible that such an ailment contributed to the increase of the blood volume, although we can not be sure that cardiac failure was one of the causes of hypervolemia in our patients, because the patients suffering from it were those with the highest degrees of anoxemia.

Venous Pressure.—The results show that the venous pressure was markedly elevated in only four patients, and these patients had cardiac failure (Fig. 8).

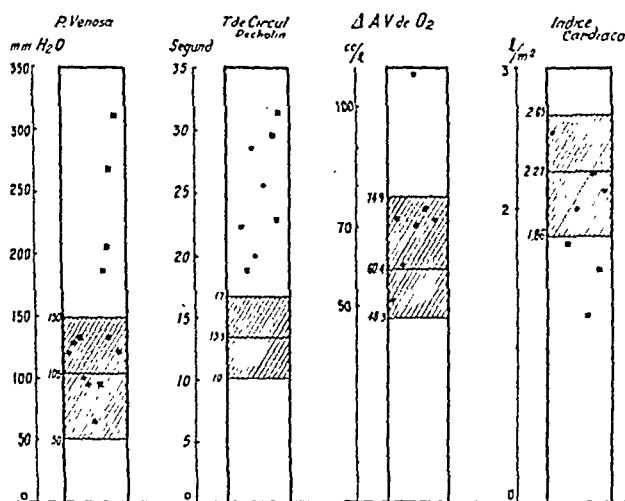


Fig. 8.—Venous pressure, circulation time, arteriovenous oxygen difference, and cardiac index in patients with Ayerza's syndrome. In circles and squares are shown the individual values found in patients with and without cardiac failure, respectively. The striped zones represent the normal limits.

These results coincide with those of Oppenheimer and Hitzig²¹ and of Kaltreider.¹⁸ Although, from the analysis of a large number of patients, it has been concluded that in those with advanced emphysema and with noticeable

variations of the pleural pressure, the venous pressure has a tendency to be elevated in the absence of cardiac failure.^{19,22} This increase may reach the maximum normal limits and even surpass them (personal data).

Circulation Time.—Decholin time was greater than 20 seconds in all the patients but one. Ether time was normal in only one patient; in all the other patients it was prolonged. As was expected, the most prolonged circulation times were found in those patients with cardiac failure. No relation was noted between the venous pressure and the circulation time. Our results coincide with those obtained by Jimenez Diaz, Agesta, and Alemany.¹⁷ They do not agree, however, with those found by Weiss and Blumgart,³¹ or by Oppenheimer and Hitzig²¹ in patients with pulmonary fibrosis and emphysema. These slight variations have no particular significance because our study has been made on a special group of patients with marked polycythemia and variations of the blood volume, which explain the delay found in the circulation time.

Cardiac Output.—This was studied in seven patients in whom the amplitude of the vital capacity, as well as the conditions of the respiratory mechanisms, permitted the use of Grollman's four-sample method with probabilities of success.

The results given in Fig. 8 show that in the patients who had only respiratory insufficiency, the cardiac output was within normal limits despite the existence of pulmonary alteration, anoxemia, or polycythemia. These results coincide with those found by Ayerza, Solari, and Berconsky³ and by Arrillaga, Berconsky, and Taquini² which proved that the minute output is normal in patients with the Ayerza's syndrome without cardiac failure. On the contrary, in those patients with cardiac insufficiency the minute output showed rather diminished values. This fact suggests a direct relation between the heart's functional capacity and the cardiac output; this relation is similar to that found in other heart diseases studied by Suarez, Fasciolo, and Taquini.²⁸ This might also be the cause of the diminution of the cardiac output found in the cases studied by Cossio and Berconsky,⁸ by Berconsky,⁴ and by Capdehourat.⁶

Discussion.—These results show that patients with Ayerza's syndrome have a normal cardiac output, a marked increase of the blood volume, an increase of the circulation time, and a normal or slightly modified venous pressure. The heart would have to increase its work very much in order to maintain a normal minute output, because there is a marked increase in the blood's viscosity caused by the polyglobulia. Since this did not happen in our patients, because the arterial pressure did not rise in every case, we have to admit that there exists a mechanism of adaptation. The permanent dilatation of the arterial and capillary bed is immediately suggested as the obvious explanation. This hypothesis is supported by the fact that the increase of the blood volume as well as that of the erythrocytes and the hemoglobin was in relation to the anoxemia. This adaptation would permit a great diminution of the blood's velocity without modifying the minute output and the arteriovenous difference¹ (Fig. 9). This is the reason why, in our patients, the time needed by the blood to complete its circuit (time is calculated by dividing the minute output by the blood volume)

was almost twice as long as the time needed in normal persons. In spite of this, the arteriovenous difference was normal, thus showing that the blood flow in the unit of time was normal. The diminution of the blood's velocity, determined by the increase of the vascular bed and the blood volume, would permit the maintenance of the heart's volume output without increasing the peripheral resistance; that is, without increasing the heart's work. This circulatory equilibrium is one of the most interesting known mechanisms of adaptation; it explains how these patients can tolerate the disorders produced by the hyperglobulia without much inconvenience.

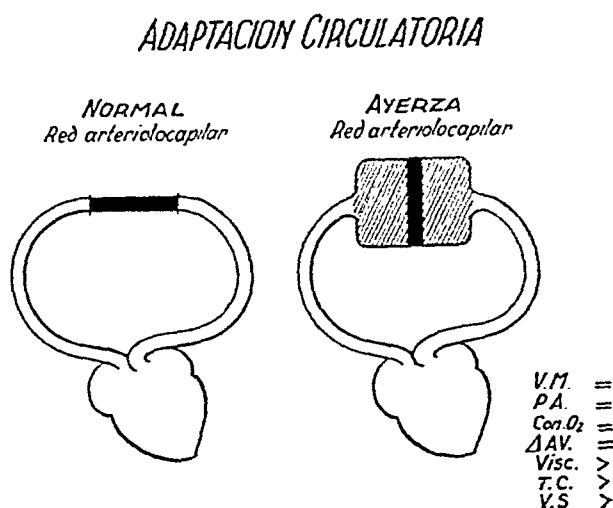


Fig. 9.—Diagram representing the circulatory adaptation in Ayerza's disease. It is noticeable that the greater the vascular bed and the blood volume, the less the velocity necessary to maintain a normal blood flow.

On the other hand, the increase of the hemoglobin's capacity has an important role in order to maintain a normal quantity of oxygen carried by the blood despite the existence of the unsaturation. This adaptation of the blood to anoxemia and the previously mentioned circulatory adaptations almost compensate for the changes in the arterial blood caused by the alveolar hypoventilation. As a result, the O₂ pressure of the venous blood is very near normal values; the state of the venous blood can be considered to show the changes going on in the tissues (Table III).

All these facts explain why patients with Ayerza's syndrome are able to maintain a rather normal function of their organs in spite of the existence of such accentuated arterial anoxemia. It also explains why their hearts maintain their functions without any further clinical signs of myocardial anoxemia; and why these patients develop mostly right heart insufficiency as a result of hemodynamic alterations provoked by pulmonary ailments.

TABLE III. OXYGEN AND CARBON DIOXIDE PRESSURES AS WELL AS pH OF ARTERIAL AND VENOUS BLOOD FROM PATIENTS WITH AYERZA'S SYNDROME COMPARED WITH MEAN NORMAL VALUES

	ARTERIAL BLOOD			MIXED VENOUS BLOOD		
	NORMALS	AYERZA'S SYNDROME		NORMALS	AYERZA'S SYNDROME	
		WITHOUT CARDIAC INSUFFICIENCY	WITH CARDIAC INSUFFICIENCY		WITHOUT CARDIAC INSUFFICIENCY	WITH CARDIAC INSUFFICIENCY
pO ₂ mm. Hg	95	48.7	47.7	35	31.7	28.0
pCO ₂ mm. Hg	41	55.4	53	49	60.5	62
pH	7.40	7.34	7.33	7.36	7.32	7.31

CONCLUSIONS

1. Studies made on sixteen patients with Ayerza's syndrome have enabled us to demonstrate the existence of the following alterations in all patients: (a) alveolar hypoventilation, (b) diminution of oxygen tension in the arterial blood, (c) increase of the carbon dioxide tension, (d) diminution of pH, (e) hemoglobin increase, (f) increase of blood volume, and (g) increase of the circulation time.

Arterial blood pressure, cardiac output, and arteriovenous oxygen difference showed no change directly attributable to the hemo-respiratory alterations.

2. Alveolar hypoventilation, as well as inadequate distribution of the gases in the lungs, easily explains the anoxemia observed in most of the patients studied.

3. Anoxemia was also fundamental in producing hemoglobin and blood volume increase.

4. Increase of hemoglobin held the amount of oxygen in the blood in quantities near normal, even though a marked decrease of oxygen tension existed.

5. Although blood velocity was decreased, an increase in blood volume permitted normal arteriovenous difference and cardiac output.

6. Decrease in blood velocity and increase in the volume of the vascular bed in patients with Ayerza's syndrome explains how the heart can maintain normal minute output and arterial blood pressure within normal limits in spite of the presence of a marked increase in the viscosity of the blood.

REFERENCES

1. Altschule, M. D., Volk, M. C., and Henstell, H.: *Am. J. M. Sc.* 200:478, 1940.
2. Arrillaga, F. C., Berconsky, I., and Taquini, A. C.: *Rev. Ascc. méd. argent.- Soc. Med. Internat.* 6:542, 1930.
3. Ayerza, L., Solari, L. A., and Berconsky, I.: *Rev. Asoc. méd. argent.-Soc. Med. Internat.* 6:511, 1930.
4. Berconsky, I.: *Semana méd.* 1:1569, 1933.
5. Bruns, O.: *Med. Klin.* 2:1524, 1910.
6. Capdehourat, E. L. Buenos Aires, 1934, Aniceto López.
7. (a) Christie, R. V.: *J. Clin. Investigation* 11:1099, 1932.
(b) Christie, R. V.: *J. Clin. Investigation* 13:295, 1934.
8. Cossio, P., and Berconsky, I.: *Semana méd.* 2:917, 1932.
9. Darling, R. C., Courmand, Q., and Richards, D. W.: *J. Clin. Investigation* 23:55, 1944.
10. Dill, D. B., Daly, C., and Forbes, W. H.: *J. Biol. Chem.* 117:569, 1937.
11. Gibson, J. G., and Evans, W. A.: *J. Clin. Investigation* 16:301, 1937.
12. Grollman, A.: *Am. J. Physiol.* 88:432, 1929.
13. Henderson, L. J., Bock, A. V., Field, H., and Stoddard, J. L.: *J. Biol. Chem.* 59:379, 1924.
14. Hoover, C. F., and Taylor, L.: *Arch. Int. Med.* 15:1, 1915.
15. Houssay, B. A., and Berconsky, I.: *Acad. Nac. Med. Bs. As. Conferencias* 2:91, 1932;
Presse méd. 40:1759, 1932.
16. Hurtado, A., Merino, C., and Delgado, E.: *Arch. Int. Med.* 75:285, 1945.
17. Jimenez Diaz, C., Agesta, A., and Alemany, M.: *Rev. Clin. españ.* 5:413, 1942.
18. Kaltreider, N. L.: *Internat. Clin.* 4:221, 1938.
19. Kountz, W. B., Pearson, E. F., and Koenig, K. F.: *J. Clin. Investigation* 11:1281, 1932.
20. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: *AM. HEART J.* 16:675, 1938.
21. Oppenheimer, B. S., and Hitzig, W. M.: *AM. HEART J.* 12:257, 1936.
22. Remolar, J. M., and Caputo, G.: *An. d. Inst. invest. fis. apl. a la pat. humana* 4:289, 1942.
23. Robinson, S.: *Arbeitsphysiol.* 10:251, 1938.
24. Roelsen, E.: *Acta med. Scandinav.* 95:452, 1938.
25. Roelsen, E.: *Acta med. Scandinav.* 98:141, 1939.
26. Siebeck, R.: *Deutsches Arch. f. klin. Med.* 102:390, 1911.
27. Sonne, C.: *Acta med. Scandinav. supp.* 59, p. 348, 1934.
28. Suarez, J. R. E., Taquini, A. C., and Fasciolo, J. C.: *AM. HEART J.* 32:339, 1496.
29. Van Slyke, D. D., Sendray, J., Jr., Hastings, A. B., and Neill, J. M.: *J. Biol. Chem.* 78:765, 1928.
30. Weiss, R.: *Ztschr. f. d. ges. exper. Med.* 61:357, 1928.
31. Weiss, S., and Blumgart, H. L.: *J. Clin. Investigation* 4:555, 1927.

EFFECTS OF INTRAVENOUS INJECTION OF NICOTINE ON THE CIRCULATION

IN NORMAL PERSONS AND IN PATIENTS WITH CARDIOVASCULAR DISEASE

MARGARET N. BOYLE, M.D., RENÉ WÉGRIA, M.D., RICHARD T.
CATHCART, M.D., JOHN L. NICKERSON, PH.D., AND ROBERT L. LEVY, M.D.
NEW YORK, N. Y.

THERE is ample evidence that the important ingredient of tobacco smoke, with respect to its action on the cardiovascular system, is nicotine.¹ Other toxic constituents, such as the pyridine bases, hydrocyanic acid, and ammonia, are present in amounts so small that they exert no appreciable effects. The concentration of carbon monoxide in the blood after smoking, except in extreme instances, does not reach sufficiently high levels to embarrass the circulation at ordinary altitudes.² By observing the effects of nicotine after intravenous injection, any possible action of these other substances is eliminated and no factors are present which might induce reflex disturbances, such as irritation of the mucous membranes or the act of inhalation. The results of such a study cannot be translated into terms directly applicable to the smoking of tobacco, but they furnish information concerning the immediate response of the heart and circulation to the most active substance absorbed from the smoke.

MATERIAL, PROCEDURE, AND METHODS

Clinical Material (Table I).—Observations were made on forty-six subjects. Of these, eighteen were normal persons ranging in age from 22 to 74 years; the average was 32.7 years. Eleven were smokers and seven were nonsmokers. There were twenty-four patients with coronary heart disease. Of these, twenty suffered from attacks of anginal pain and ten had hypertension, and in four a healed myocardial infarct was known to be present. The ages ranged from 40 to 78 years, with an average of 55.9 years. Seventeen were smokers and seven were nonsmokers. There were four patients with peripheral vascular disease. The diagnosis was Raynaud's disease in two, thromboangiitis obliterans in one, and scleroderma with gangrene of the fingers in one. The ages ranged from 21 to 50 years, with an average of 39.5 years. Three were smokers and one was a nonsmoker.

From the Departments of Medicine and Physiology, College of Physicians and Surgeons, Columbia University, and the Medical Service, Presbyterian Hospital.

This study was aided by a gift from Dr. Shepard Krech.

Read, in part, at the Fifty-ninth Session of the Association of American Physicians, Atlantic City, N. J., May 28, 1946.

Received for publication Sept. 17, 1946.

To these forty-six individuals, sixty-four intravenous injections of nicotine were given.

TABLE I. SUMMARY OF CLINICAL MATERIAL

Number of subjects		46
Number of nicotine injections		64
Determinations of cardiac output		18
Normals		18
Smokers	11	
Nonsmokers	7	
Ages, 22 to 74; average, 32.7 years		
Coronary heart disease		24
With anginal pain	20	
With hypertension	10	
With healed infarction	4	
Smokers	17	
Nonsmokers	7	
Ages, 40 to 78; average, 55.9 years		
Peripheral vascular disease		4
Raynaud's disease	2	
Thromboangiitis obliterans	1	
Scleroderma	1	
Smokers	3	
Nonsmoker	1	
Ages, 21 to 50; average, 39.5 years		

Preparation and Dosage.—The preparation employed was nicotine bitartrate.* It was preferred to other salts because of its ready solubility in water and its stability. The bitartrate contains 32.54 per cent of nicotine, 60.23 per cent of tartaric acid, and 7.23 per cent of water.³

The dosage used was 2 mg. dissolved in 2 c.c. of water. The amount of alkaloid contained in 2 mg. of bitartrate is approximately 0.6 milligram. This was injected intravenously, after mixing it with blood in the barrel of the syringe. Tests indicated that such admixture did not lessen the potency of the alkaloid. The effects of the injection of 0.5 mg. in a dog are shown in Fig. 1. This dose is about 20 per cent larger (milligrams per kilogram of body weight) than that given to the human subjects. The increase in blood pressure and heart rate, as well as the acceleration in respiration, are clearly seen.

Procedure.—All observations were made with the patients in the recumbent position. The needle was inserted into the vein several minutes before the injection was given. Repeated recordings were made of the heart rate and of the systolic and diastolic blood pressures. The cardiac output was determined by means of the ballistocardiograph devised by Nickerson and Curtis.⁴ According to this technique, a change of 10 per cent may be considered significant. Determinations of the blood sugar were made by the method of Folin,⁵ with the subjects in the fasting state.

Two control electrocardiograms were made and records were taken at frequent intervals after the injection of nicotine. In addition to the usual limb

*Nicotine bitartrate in aqueous solution was supplied in ampoules by the Abbott Laboratories, North Chicago, Ill., through the courtesy of Dr. J. F. Biehn, Director of the Department of Medicine.

leads, precordial Lead IV F was taken. Changes were regarded as "slight" if there was (1) decrease in the amplitude of the T wave, in any lead, of 1 mm. or more, or (2) deviation of the RS-T segment, in any lead, of less than 1 millimeter. Changes were considered "significant" if there was (1) complete or partial reversal in the direction of T₁, T₂, or T₄F, or (2) deviation of the RS-T segment, in any lead, of 1 mm. or more.

Any symptoms of which the patient complained were noted.

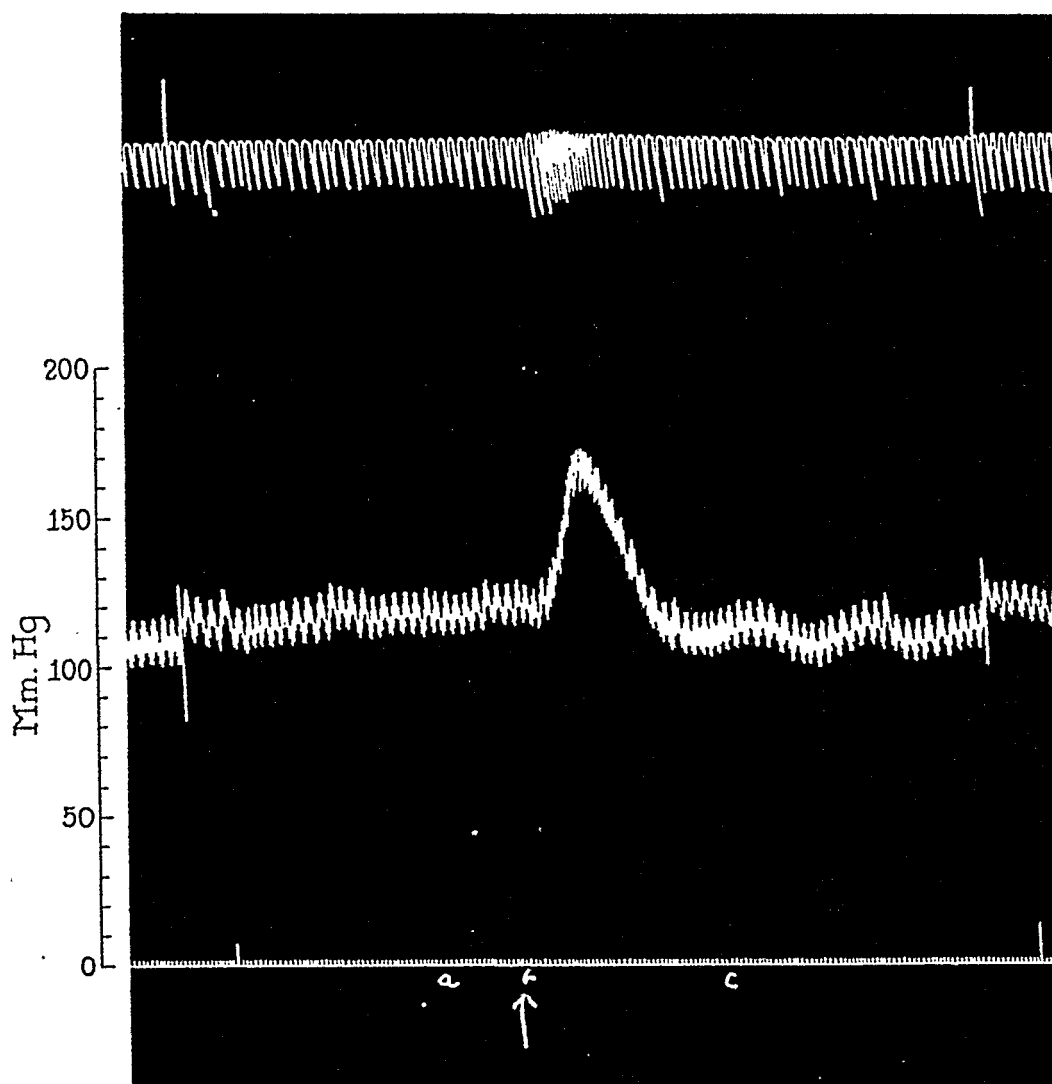


Fig. 1.—Dog, weight 14.5 kilograms. Anesthesia induced by morphine, followed by 1.5 c.c. per kilogram of 20 per cent sodium barbital, injected intravenously. Upper tracing, respiration. Lower tracing, blood pressure. Time, in seconds. At *b*, intravenous injection of 0.5 mg. nicotine bitartrate.

RESULTS

The results were tabulated for the three groups of individuals studied (Table II). In each group a further subdivision was made into smokers and non-smokers. The analysis was designed to indicate the degree of change which occurred in the indexes employed and to make possible a comparison of the effects in the three groups of cases. The statistical significance of the averages was determined by comparing them with their standard error; this depends upon the number of readings and their range of variation.

In all of the analyses no significant differences were observed between smokers and nonsmokers, so that in the discussion which follows these categories have been combined.

Heart Rate (Table II).—The average change in heart rate in normal individuals was +19 beats per minute; the range was from 0 to +57. The average change in the patients with coronary heart disease was +14; the range was from -12 to +42. In those with peripheral vascular disease, the average change was +12; the range was from +8 to +28. There were no significant differences in the averages of the three groups.

TABLE II. AVERAGES OF THE MAXIMAL CHANGES OBSERVED IN HEART RATE, BLOOD PRESSURE AND CARDIAC OUTPUT IN THREE GROUPS OF INDIVIDUALS AFTER INTRAVENOUS INJECTION OF 2 MG. NICOTINE BITARTRATE

	NORMALS		CORONARY HEART DISEASE		PERIPHERAL VASCULAR DISEASE	
	NUMBER CASES	AVERAGE	NUMBER CASES	AVERAGE	NUMBER CASES	AVERAGE

Heart Rate (Beats per minute)

Smokers	11	21	17	15		
Nonsmokers	7	16	7	11		
Totals	18	19	24	14	4	12

Systolic Blood Pressure (mm. Hg)

Smokers	11	10	17	12		
Nonsmokers	7	11	7	20		
Totals	18	10	24	15	4	16

Diastolic Blood Pressure (mm. Hg)

Smokers	11	6	17	7		
Nonsmokers	7	10	7	13		
Totals	18	8	24	9	4	8

Cardiac Output (liters per minute), Smokers and Nonsmokers

Totals	8	1.9	7	0.8	3	1
--------	---	-----	---	-----	---	---

Systolic Blood Pressure (Table II).—In the normal subjects the average change was +10 mm. Hg; the range was from +2 to +22. In the patients with coronary heart disease, the average change was +15; the range was from +4 to +60. In those with peripheral vascular disease, the average change was +16; the range was from +2 to +50. There were no significant differences in the averages of the three groups.

Diastolic Blood Pressure (Table II).—In the normal subjects the average change was +8 mm. Hg; the range was from 0 to +20. In the patients with coronary heart disease, the average change was +9; the range was from -2 to +25. In those with peripheral vascular disease, the average change was +8; the range was from 0 to +20. There were no significant differences in the averages of the three groups.

Cardiac Output (Table II).—In the normal group the average change was +1.9 liters per minute; the range was from -0.4 to +7.5. There was a significant rise in six subjects and a slight fall in two. In the patients with coronary heart disease, the average change was +0.8; the range was from -1.9 to +2.3. There was a significant rise in five patients and a slight fall in two. In those with peripheral vascular disease, the average change was +1.0; the range was from +0.2 to +1.8. There was a significant rise in three patients; in the fourth patient no determinations of output were made. There were no significant differences in the averages of the three groups.

Electrocardiogram.—Electrocardiograms were taken in sixteen of the normal individuals. There was no change in nine, a slight change in seven, and a significant change in none. In the patients with coronary heart disease, there was no change in eighteen, a slight change in three, and a significant change in three. In those with peripheral vascular disease, there was no change in two, a slight change in one, and a significant change in one. The patient in this latter group whose electrocardiogram showed a significant change was a woman 47 years of age with scleroderma and ulceration of the fingers, in whom coronary heart disease was also present. The anoxemia test in this patient was positive. In two of the patients showing significant changes, the control electrocardiogram was abnormal; in two it was normal.

Symptoms.—Symptoms occurred in thirteen normal subjects, sixteen patients with coronary heart disease, and three with peripheral vascular disease. There was great individual variation in their number and severity. Immediately after the injection was completed, almost every subject took several deep breaths. In all groups, the commonest complaint was dizziness. Other sensations were tingling and faintness. Nausea occurred three times. Anginal pain occurred in two of the patients in the coronary group in whom significant alterations in the electrocardiogram were observed.

One unusually severe reaction was encountered. This occurred in a normal man, 24 years of age. He had never smoked but could give no particular reason for not having done so. The control heart rate was 64 per minute; the blood pressure was 105/85. After intravenous injection of the usual dose of nicotine,

he perspired profusely and became pale and cold. In a few minutes he was nauseated and vomited. The pulse became thready and the blood pressure, for a short time, was not obtainable. He then retched for five minutes, felt nauseated for an hour, and was weak for the remainder of the morning. Because of the violence of the reaction, electrocardiograms were not taken and the cardiac output could not be determined. His record, therefore, is not included in the series.

Blood Sugar.—Eight determinations were made in seven subjects, of whom three were normal and four were patients with coronary and hypertensive heart disease (Table III). A control sample was taken, and blood was drawn three and ten minutes after the injection of nicotine. No consistent variations were found, although there were some fluctuations, both upward and downward, which were greater than the error inherent in the method. In one patient, P., the control reading on one occasion was 111 mg. per cent; three minutes after nicotine injection, the level rose to 133, an increase of almost 20 per cent. On another occasion, the control reading in the same patient was 86; ten minutes after nicotine injection, the level fell to 68, a decrease of 20 per cent. In none of the subjects was there an apparent correlation between the direction or degree of change in the blood sugar level and variations in blood pressure, heart rate, or the form of the electrocardiogram.

DISCUSSION

Careful studies of the nicotine content of tobacco smoke have been made by Baumberger.⁶ He found that the amount of nicotine in the puffed smoke of one cigarette is about 4.5 milligrams. Four cigarettes are equivalent to one mild cigar. The frequency of puffing determines the rate of absorption.

Approximately 66.7 per cent of the smoke and, presumably, the nicotine drawn into the mouth, are absorbed. If the smoke is inhaled, 88.2 per cent are absorbed. Assuming 66.7 per cent absorption and a rate of puffing of five per minute, the dosage rate of nicotine from cigarette smoke would be 0.46 mg. per minute, or 27.5 mg. per hour. With inhalation, and hence absorption of 88.2 per cent, the dosage rate would be 0.6 mg. per minute, or 36 mg. per hour.

On the basis of these figures, about 3 mg. of nicotine are absorbed from a cigarette if not inhaled, and 4 mg. if the smoke is drawn into the lungs. It has already been mentioned that 2 mg. of the bitartrate, which was the amount injected in each subject, contain 0.6 mg. of nicotine alkaloid. The dose employed, therefore, was relatively small. But it was introduced directly and quickly into the circulation and was large enough to cause reactions which were readily measurable.

The most striking feature apparent from our results is the marked individual variation in response observed in members of all groups studied. Examples are given in the following brief clinical notes and are illustrated.

CASE 1.—D. P. was a normal woman, 24 years of age, who never inhaled and limited herself to two cigarettes a week because smoking caused palpitation and heartburn. After injection of nicotine, there was a sharp rise in blood pressure, heart rate, and cardiac output (Fig. 2). The

TABLE III. EFFECT OF INTRAVENOUS INJECTION OF 2 MG. NICOTINE BITARTRATE ON BLOOD SUGAR IN RELATION TO CHANGES IN THE CIRCULATION

SUBJECT	DIAGNOSIS	BLOOD SUGAR (MG. PER CENT)				MAXIMAL CIRCULATORY CHANGES			ELECTROCARDIO- GRAPHIC CHANGES	
		CONTROL	3 MIN.	10 MIN.	MAXIMAL CHANGE	SYSTOLIC BLOOD PRESSURE (MM. HG)	DIASTOLIC BLOOD PRESSURE (MM. HG)	HEART RATE (BEATS PER MIN.)	SLIGHT	SIGNIFI- CANT
D.	Normal	114	103	101	-13	+10	+10	+12	0	0
Ca.	Normal	83	85	74	+2:-9	+15	+20	+2	0	0
K.*	Normal	88	93	87	+5:-1.	+15	+12	+48	+	-
M.	Coronary heart disease	124	121	120	-4	+10	+2	+8	0	0
E.	Coronary and hypertensive heart disease	78	89	77	+11:-1	+18	+10	+20	-	+
Ch.	Hypertensive heart disease; syphilitic aortitis	133	118	123	-15	+10	+8	+16	0	0
P.	Coronary and hypertensive heart disease; healed cardiac infarct	111	133	117	+22	+4	0	+4	0	0
		86	79	68	-18	+10	+8	+8	0	0

*Received only 1 mg. nicotine because of sharp reaction in previous tests.

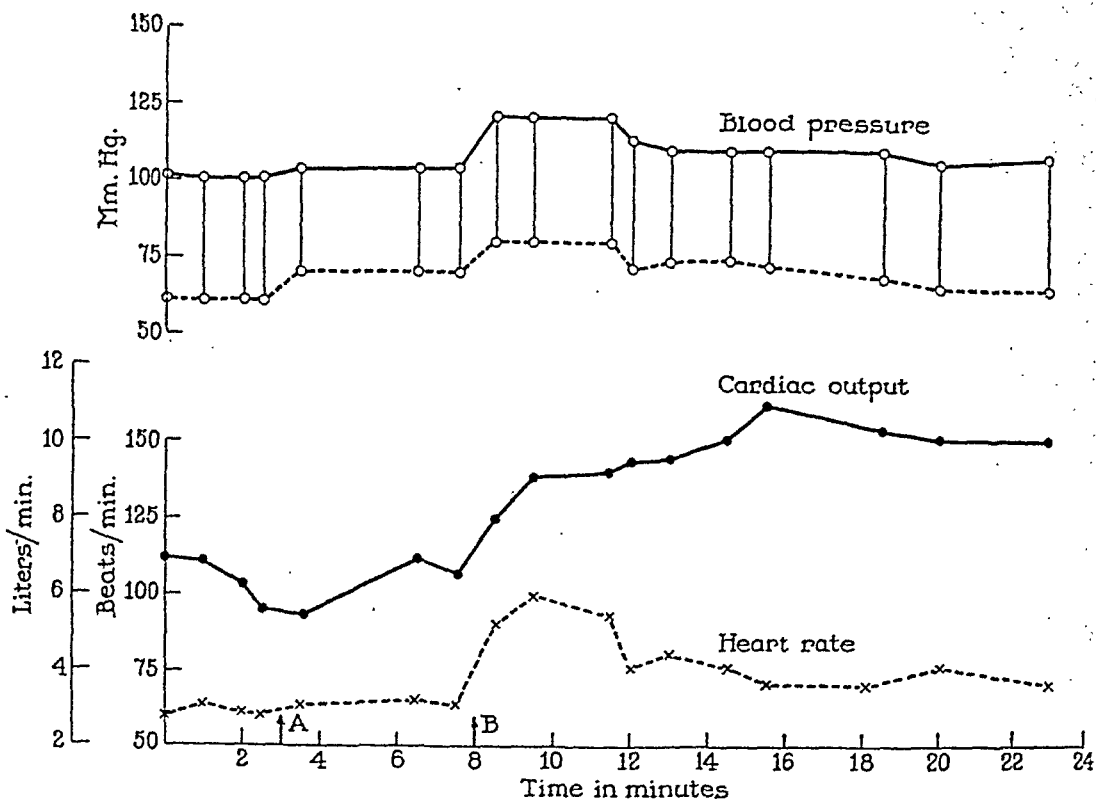


Fig. 2.—Case 1. Normal woman, 24 years of age. At A, needle injected into vein. At B, 2 mg. nicotine bitartrate injected. Became dizzy and faint.

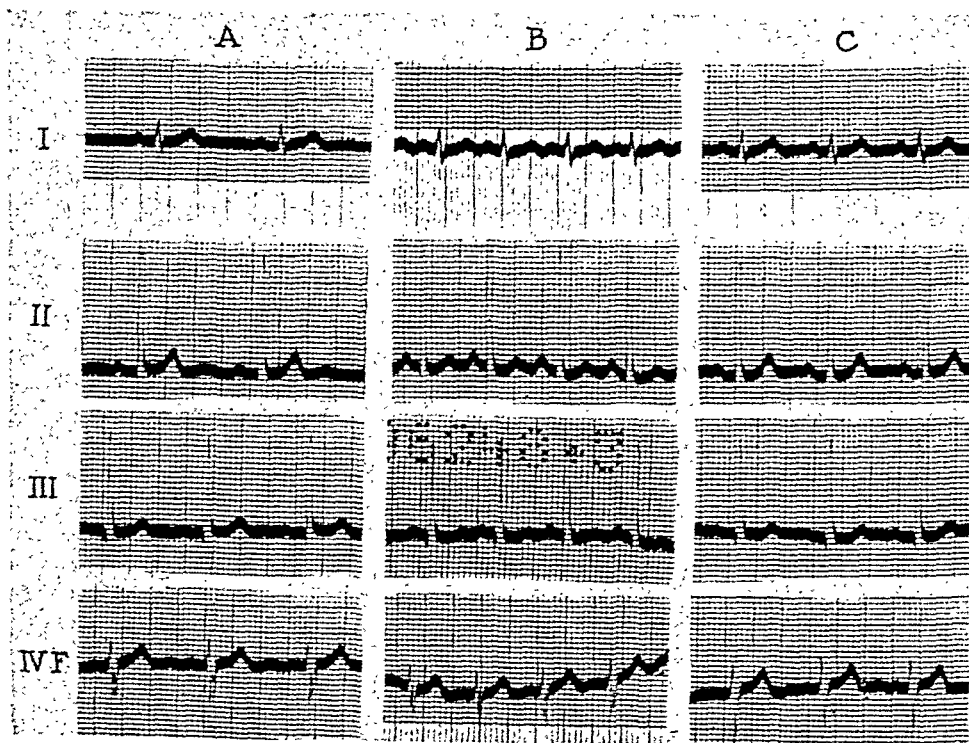


Fig. 3.—Case 1. Normal woman, 24 years of age. A, Control. Needle in vein. Rate, 88; blood pressure 110/65. B, One minute after injection of 2 mg. nicotine bitartrate. Rate, 136; blood pressure 130/85. Became dizzy and faint. C, Nine minutes after injection. Rate 98; blood pressure, 115/65.

increase in cardiac output was sustained throughout the period of observation. She complained of dizziness and faintness.

The control electrocardiogram was normal. After nicotine injection, it showed tachycardia, lowering of the T waves in all leads, and depression of the RS-T segments in Leads I, II, and III (Fig. 3). The changes in form were slight.

CASE 2.—R. D. was a normal man, 26 years of age, who had smoked twenty cigarettes daily for eight years and always inhaled. The control electrocardiogram was normal. After nicotine injection (Fig. 4) there was a slight and very transitory rise in blood pressure. The heart rate increased a few beats. The cardiac output fell. There were no symptoms. The electrocardiogram showed no changes. Injection of 4 mg. of nicotine bitartrate caused no greater effects.

CASE 3.—H. E. was a woman, 66 years of age, with coronary and hypertensive heart disease who had been subject to attacks of anginal pain for seven years. She had never smoked. The control electrocardiogram showed regular sinus rhythm. The T waves in the limb leads were of low amplitude but were upright. There was sharp inversion of T_{aF} and slight depression of the RS-T segments in Leads I, II, and IV F.

Several minutes after the injection of nicotine, she experienced severe precordial pain which radiated down the left arm. This increased in severity and continued for eight minutes, when nitroglycerin was given and afforded immediate relief. The changes in the electrocardiogram were accentuated in that T₁ became diphasic and the depressions of RS-T, particularly in Lead IV F, became more marked. The total increase in RS-T depression measured 3.5 millimeters. Twelve days later the same dose of nicotine caused the heart rate to rise from 80 to 110 beats per minute and the blood pressure, from 150/90 to 156/106. The cardiac output increased from 5.1 to 7.4 liters per minute (Fig. 5). There was slight precordial pain, but this symptom required no medication. The same changes were observed in the electrocardiograms.

Three months later the patient was having fewer anginal attacks, having spent the early weeks of the intervening period in the hospital and the latter part in a convalescent home. After nicotine injection, the heart rate rose from 84 to 100 beats per minute and the blood pressure, from 128/78 to 144/88. No pain was felt. The form of the control electrocardiogram was as previously described and nicotine caused the same changes.

CASE 4.—B. C. was a man, 53 years of age, with coronary and hypertensive heart disease. He had suffered from attacks of anginal pain for three years, and one year previously had been in the hospital because of cardiac insufficiency. He had smoked twenty cigarettes daily and an occasional cigar for years, but for two months had cut down to two cigars daily.

The control electrocardiogram showed regular sinus rhythm with an occasional ventricular premature beat. Left axis deviation was marked. The T wave was inverted in Lead I, upright in Leads II and III, and diphasic in Lead IV F. He had been taking maintenance doses of digitalis for some time, and some of these alterations may have been due to the action of this drug.

Nicotine injection caused no change in heart rate and a slight rise in systolic blood pressure. The cardiac output was decreased (Fig. 6). The electrocardiogram was unchanged.

Observations on the effects of smoking and of nicotine injection on the circulation have recently been reported by Roth, McDonald, and Sheard⁷; they also reviewed earlier work. The electrocardiograms of normal persons have shown lowering of the T waves,⁸ and sometimes inversion in Leads II and III.⁹ Of particular interest are two cases of coronary heart disease described by Wilson and Johnston.¹⁰ In both patients, after smoking one or two cigarettes, changes occurred in the electrocardiogram resembling those seen in the early stages of infarction of the posterior wall of the heart. Because of the lack of parallelism between the magnitude of the changes and cardiac work, as represented by increase in heart rate and blood pressure, Wilson and Johnston concluded that nicotine or some other ingredient of tobacco smoke sometimes induces coronary

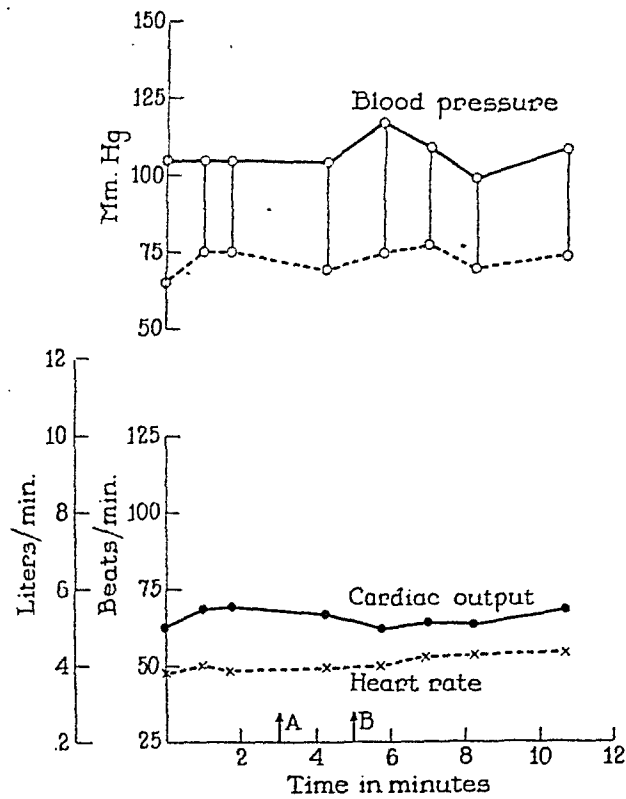


Fig. 4.—Case 2. Normal man, 26 years of age. At A, needle inserted into vein. At B, 2 mg. nicotine bitartrate injected. No discomfort.

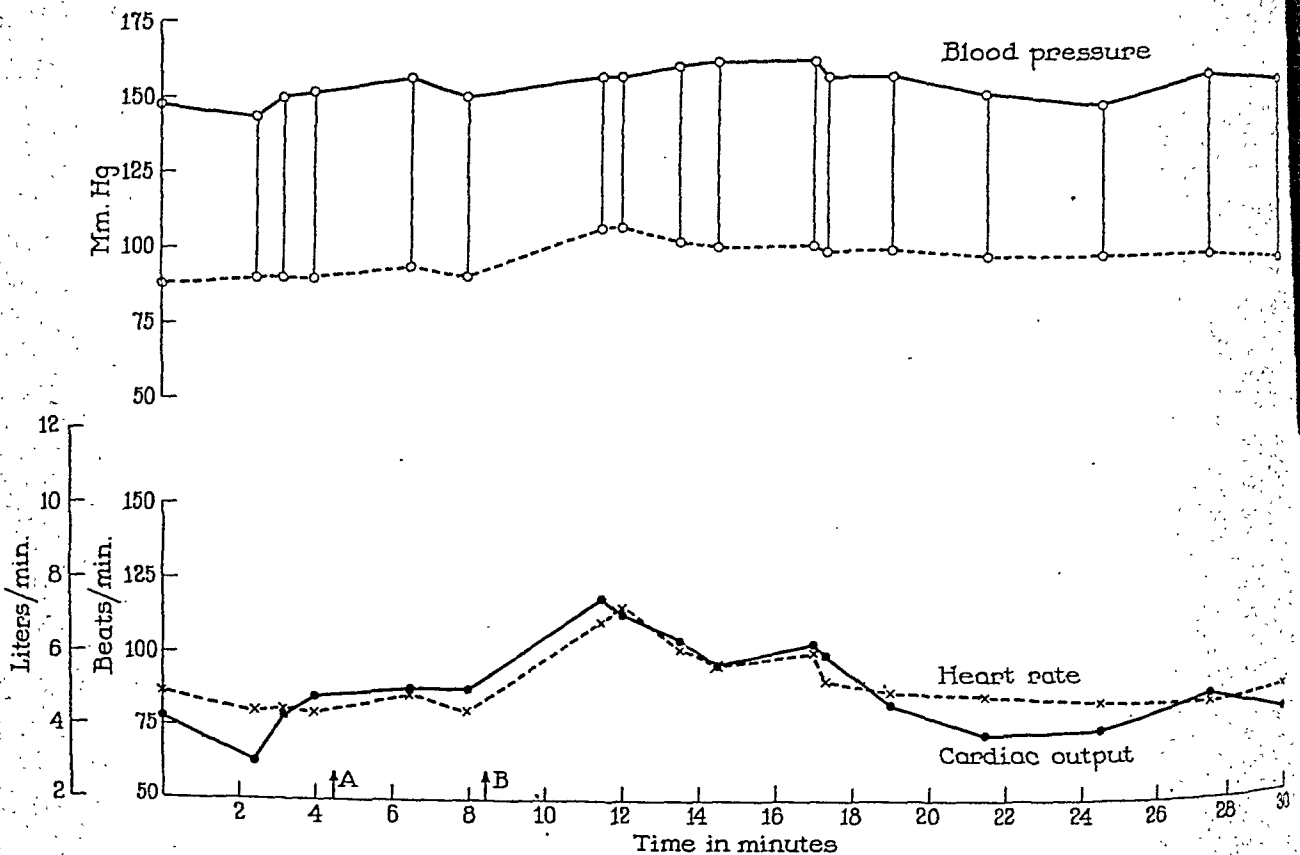


Fig. 5.—Case 3. Woman, 66 years of age, with coronary heart disease and anginal pain. At A, needle inserted into vein. At B, 2 mg. nicotine bitartrate injected. Complained of precordial pain, which was relieved by nitroglycerine.

spasm in patients subject to anginal attacks. Graybiel and collaborators⁹ and Pickering and Sanderson,¹¹ on the other hand, were inclined to ascribe cardiac pain induced by smoking to the increased work of the heart rather than to constriction of the coronary arteries.

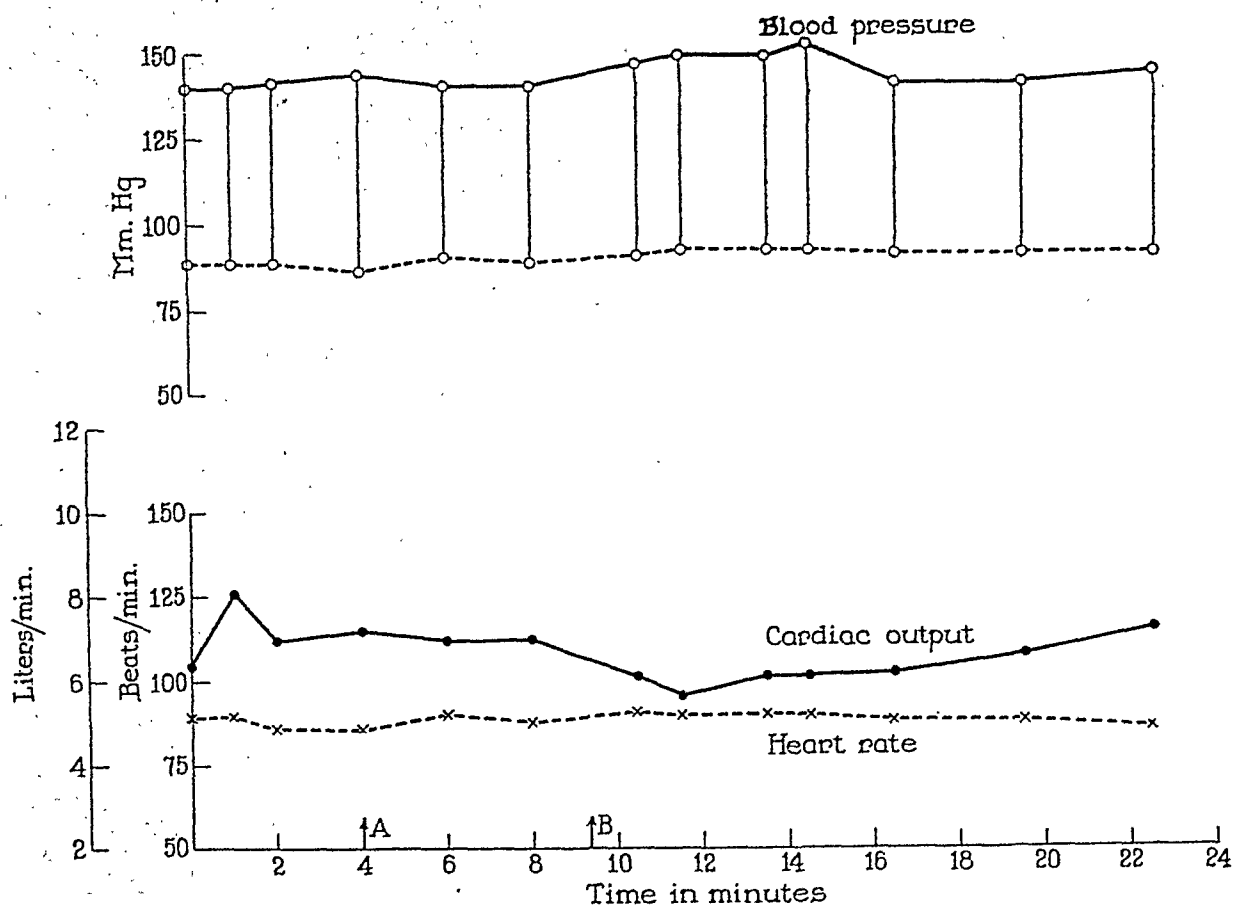


Fig. 6.—Case 4. Man, 53 years of age, with hypertensive cardiovascular disease and anginal pain. At A, needle inserted into vein. At B, 2 mg. nicotine bitartrate injected. No pain.

Significant alterations in the form of the electrocardiogram after nicotine injection were observed in four of our patients with coronary heart disease. Three of them were subject to anginal attacks; in only two, however, did pain accompany the electrocardiographic changes. The man (G. M.) whose tracings are shown in Fig. 7 was treated at the hospital for posterior cardiac infarction three months before these observations were made. Fifteen minutes after nicotine injection, the increase in heart rate was twelve beats per minute; the systolic blood pressure rose only 8 mm. Hg and the diastolic, 2 millimeters. He did not experience pain. Yet the changes in the electrocardiogram were well defined, with depression of the RS-T segments in Leads I, II, and IVF and partial inversion of the T waves in the precordial lead. These changes were similar to the ones caused by induced anoxemia in patients with coronary insufficiency.¹²

In one other patient with significant electrocardiographic changes, the increase in heart rate was slight. In a third patient the rise in systolic blood pressure was only 4 mm. Hg, and in diastolic, 12, but the heart rate rose thirty beats and the cardiac output increased 2.3 liters per minute. Only in patient

G. M. were the increases in both heart rate and blood pressure so small that they hardly could be credited with augmenting cardiac work to a degree corresponding to the changes in the electrocardiogram. It seems reasonable to infer, therefore, that nicotine may induce coronary insufficiency by constricting the coronary arteries or by increasing the work of the heart. Probably both mechanisms are concerned.

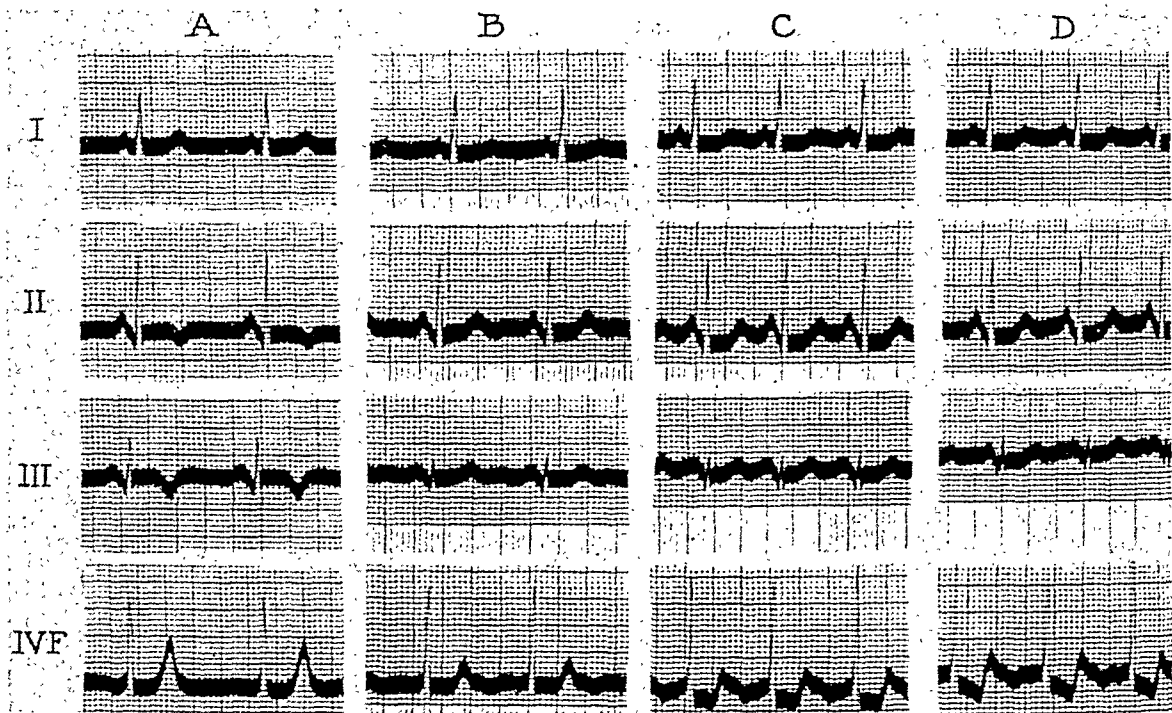


Fig. 7.—G. M. Man, 50 years of age, with coronary heart disease and anginal pain. Moderate smoker. A, Two weeks after cardiac infarction. Nicotine study made three months later. B, Control. Needle in vein. Rate, 90; blood pressure, 140/80. C, Two minutes after injection of 2 mg. nicotine bitartrate. Rate, 120; blood pressure, 144/86. D, Fifteen minutes after injection. Rate, 102; blood pressure 148/82. No anginal pain; complained of dizziness and tingling.

Determinations of cardiac output after smoking were made in five normal persons by Grollman,¹³ using the acetylene method. His results, like ours, were variable, with increases ranging from 0.1 to 1.3 liters per minute. The largest increase was observed in an habitual cigarette smoker after he had smoked three cigars. Another cigarette smoker, after smoking two cigars, showed an increase in output of only 0.1 liter per minute. Moderate smoking yielded intermediate values.

In 1912, Cannon, Aub, and Binger¹⁴ demonstrated, in cats, that the intravenous injection of nicotine, in doses of 3.5 to 7.5 mg., resulted in augmented adrenal secretion. Such doses are comparatively much larger than those employed by us. It was of interest to know whether added liberation of epinephrine might play a part in causing the circulatory changes observed. In view of the technical difficulty in determining the amount of epinephrine in the blood, a rise in the level of the blood sugar appeared to offer an indirect though crude

indicator of adrenal stimulation, for it has long been known that an increase of epinephrine in the blood induces hyperglycemia.

Widely different effects on the level of the blood sugar after smoking have been described by various investigators and these have been summarized by Dill and associates.¹⁵ Increases of 10 to 40 per cent after one cigarette, and a decrease of 27 per cent after one cigar, have been reported. Other authors have noted both increases and decreases.

Dill's group made frequent determinations after the inhalation of the smoke of one cigarette in the course of five to ten minutes. The amount of nicotine absorbed was thus comparable to the dose injected in our studies. Nine-tenths of the observations, in their ten fasting subjects, were within 5 per cent of the rest level. The fluctuations in our subjects were wider, but, in both series there was no consistent trend, either upward or downward.

It is possible that the amount of epinephrine effective in causing changes in the cardiovascular system is smaller than that necessary to raise the blood sugar. Because of the relatively small dose of nicotine injected and the failure to induce hyperglycemia, it seems improbable that an increase in adrenal secretion was responsible for the circulatory reactions observed. In any case, these were initiated by nicotine.

SUMMARY AND CONCLUSIONS

1. Intravenous injections of 2 mg. of nicotine bitartrate were given to forty-six subjects. These included eighteen normal persons, twenty-four patients with coronary heart disease, and four with peripheral vascular disease. Observations were made on changes in the heart rate, blood pressure, cardiac output, and electrocardiogram. The symptoms produced were noted.

2. The amount of nicotine alkaloid contained in 2 mg. of the bitartrate is approximately 0.6 milligrams. This corresponds to the estimated amount of nicotine absorbed on inhaling the smoke of a cigarette five times in the course of one minute.

3. A comparison was made of the average changes observed in heart rate, blood pressure, and cardiac output in the normal group, in the patients with coronary heart disease, and in those with peripheral vascular disease. No significant differences between the three groups were apparent on statistical analysis. There was much less variation in repeated tests in the same individual than in different individuals.

4. There were no significant differences in reaction between smokers and nonsmokers in any group.

5. After the injection of nicotine, slight changes in the electrocardiogram were observed in some members of all groups. Significant changes were observed in four patients with coronary heart disease. In two of these, who suffered from spontaneous anginal attacks, pain was associated with the appearance of electrocardiographic changes.

6. In all groups, individual differences in sensitivity to nicotine were evident in the number and severity of the symptoms which followed its injection.

The most frequent complaint was dizziness. Other symptoms were tingling, faintness, and nausea. Vomiting and brief circulatory collapse occurred in one normal young man who had never smoked.

7. Nicotine injection caused no consistent variations in the level of the blood sugar in fasting subjects, although there were fluctuations both upward and downward. Because of the small dose of nicotine injected and the failure to induce hyperglycemia, it seems improbable that augmented adrenal secretion was responsible for the circulatory reactions observed. In any case, these were initiated by nicotine.

8. Variation in the effects of nicotine on the circulation is as great in patients with cardiovascular disorders as in normal persons. This variation depends to a greater extent upon individual susceptibility than upon the presence of disease.

9. In some patients with coronary heart disease, the injection of nicotine induces a state of coronary insufficiency. This may be the result of constricting the coronary arteries or of increasing the work of the heart. Probably both mechanisms are concerned.

We are indebted to Dr. John W. Fertig, Professor of Biostatistics, College of Physicians and Surgeons, Columbia University, for his help in making the statistical analyses.

REFERENCES

1. (a) Sollmann, Torald: *Manual of Pharmacology*, ed. 6, Philadelphia, 1942, W. B. Saunders Co., p. 404.
- (b) Haag, H. B.: The Physiologic Activity of Cigarette Smoke Solutions as Related to Their Nicotine Content, *J. Lab. & Clin. Med.* 25:610, 1940.
2. (a) Baumberger, J. P.: The Carbon Monoxide Content of Tobacco Smoke and Its Absorption on Inhalation, *J. Pharmacol. & Exper. Therap.* 21:23, 1923.
- (b) Hanson, H. B., and Hastings, A. B.: The Effect of Smoking on the Carbon Monoxide Content of Blood, *J.A.M.A.* 100:1481, 1933.
- (c) Barach, A. L., Eckman, Morris, and Molomut, Norman: Modification of Resistance to Anoxia With Especial Reference to High Altitude Flying, *Am. J. M. Sc.* 202:336, 1941.
3. Merck Index, ed. 5, Rahway, N. J., 1940, Merck & Co., Inc.
4. (a) Nickerson, J. L., and Curtis, H. J.: The Design of the Ballistocardiograph, *Am. J. Physiol.* 142:1, 1944.
- (b) Nickerson, J. L.: The Low Frequency, Critically-Damped Ballistocardiograph, *Federation Proc.* 4:201, 1945.
5. Folin, Otto: Two Revised Copper Methods for Blood Sugar Determination, *J. Biol. Chem.* 82:83, 1929.
6. Baumberger, J. P.: The Nicotine Content of Tobacco Smoke, *J. Pharmacol. & Exper. Therap.* 21:35, 1923.
7. Roth, G. M., McDonald, J. B., and Sheard, Charles: The Effect of Smoking Cigaretts and of Intravenous Administration of Nicotine on the Electrocardiogram, Basal Metabolic Rate, Cutaneous Temperature, Blood Pressure and Pulse Rate of Normal Persons, *J.A.M.A.* 125:761, 1944.
8. (a) Ssalischtschew, A. S., and Tschernogoroff, J. A.: Elektrokardiographische Analyse der Nicotinwirkung auf das Herz, *Ztschr. f. d. ges. exper. Med.* 64:319, 1929.
- (b) Ssalischtschew, A. S., and Tschernogoroff, J. A.: Weitere Beobachtungen über die Veränderungen im Elektrokardiogramm und im Sphygmogramm beim Menschen unter den Einfluss der Stoffe des Tabakrauches, *Ztschr. f. d. ges. exper. Med.* 78:193, 1931.
9. Graybiel, Ashton, Starr, R. S., and White, P. D.: Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, *AM. HEART J.* 15:89, 1938.
10. Wilson, F. N., and Johnston, F. D.: The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and in Kind to Those Produced by Myocardial Infarction, *Tr. A. Am. Physicians* 54:210, 1939.

11. Pickering, G. W., and Sanderson, P. H.: Angina Pectoris and Tobacco, Clin. Sc. 5:275, 1945.
12. Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: The "Anoxemia Test" as an Index of the Coronary Reserve. Serial Observations on One Hundred and Thirty-Seven Patients With Their Application to the Detection and Clinical Course of Coronary Insufficiency, J.A.M.A. 117:2113, 1941.
13. Grollman, Arthur: The Cardiac Output of Man in Health and Disease, Springfield, Ill., 1932, Charles C. Thomas, p. 159.
14. Cannon, W. B., Aub, J. C., and Binger, C. A. L.: A Note on the Effect of Nicotine Injection on Adrenal Secretion, J. Pharmacol. & Exper. Therap. 3:379, 1912.
15. Dill, D. B., Edwards, H. T., and Forbes, W. H.: Tobacco Smoking in Relation to Blood Sugar, Blood Lactic Acid and Metabolism, Am. J. Physiol. 109:118, 1934.

FRACTIONAL CIRCULATION TIMES USING FLUORESCENT TRACER SUBSTANCES

TRAVIS WINSOR, M.D., WILLIAM ADOLPH, M.D., WALTER RALSTON, M.D.,
AND GEORGE M. LEIBY, M.D.
LOS ANGELES, CALIF.

LOCALIZATION of altered cardiovascular dynamics has been difficult using the commonly employed techniques,²⁻⁵ and the clinical applications of circulation time measurements have been limited by the inability to determine minimal circulatory retardation. These obstacles can be minimized by utilizing the newer tracer methods,^{6,7} by means of which measurements to various regions of the body and measurements over longer segments of the cardiovascular system can be made. The purpose of this paper is to (1) demonstrate the use of riboflavin as a fluorescent tracer substance, (2) present a technique which renders circulation time measurements of greater clinical value, and (3) demonstrate the value of fractional circulation time measurements.

GENERAL METHOD

The technique employed was to raise a histamine wheal⁸ (0.1 c.c. of a mixture of equal parts of 1:1,000 histamine phosphate and 2 per cent procaine) on various portions of the body to which the circulation time was to be measured. The volar surface of the forearm near the antecubital fold was used for arm-to-arm times and the dorsum of the foot was used for arm-to-foot times. After approximately one minute, or during the developing phase of the wheal, a fluorescent material was injected into an antecubital vein. The time was measured from the beginning of the injection to the first appearance of yellow-green fluorescence in the periphery of the wheal. Fluorescence was excited by a 100 watt CH-4 spot ultraviolet lamp, fitted with a Corning 586 filter with maximal emission at 3,600 Å units.

Three groups of subjects were studied: (1) normal individuals, (2) those with heart disease with minimal evidence of cardiac failure, and (3) patients with marked left and right ventricular congestive heart failure. Patients with peripheral vascular disease were excluded. The room temperature was approximately 83° F. unless otherwise stipulated.

From the Cardiovascular Clinical Research Laboratory of the University of Southern California, the Los Angeles County General Hospital, and the Physiological Laboratory, Birmingham General Hospital, Veterans' Administration, Van Nuys, California.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Read at the Inter-American Congress of Cardiology, Mexico, D. F., Oct. 5-12, 1946.

A COMPARATIVE STUDY OF FLUORESCENT AGENTS USEFUL IN THE OBJECTIVE DETERMINATION OF CIRCULATION TIMES

A number of fluorescent materials were studied in vivo and in vitro. Atabrine, theophylline, certain xanthine derivatives, acriflavine, riboflavin, and fluorescein all showed some degree of fluorescence. Of these, riboflavin* and fluorescein were satisfactory for clinical use, being relatively diffusible in tissue spaces and easily visible, and giving sharp end points in a darkened room. The entire dosage of riboflavin or fluorescein could be administered in 2 c.c. of fluid. Riboflavin, however, was not painful when injected subcutaneously, and was technically easy to administer because of its transparency.

The concentration and dosage of riboflavin and fluorescein necessary for maximum fluorescence in vitro was determined by means of the fluorophotometer. Peak fluorescence of riboflavin was produced at a concentration of 8×10^{-5} moles per liter (Fig. 1). Peak fluorescence for fluorescein occurred at con-

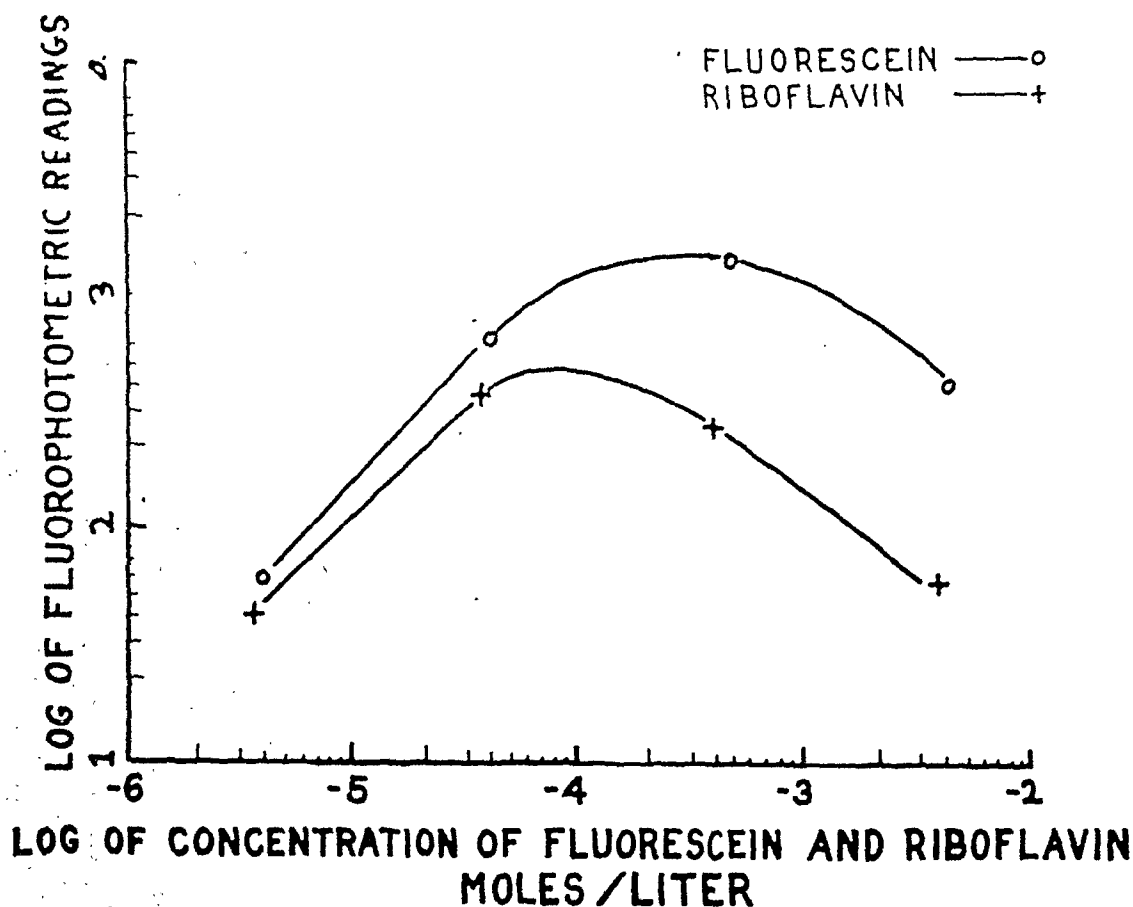


Fig. 1.—Relation between concentration of riboflavin and fluorescein and degree of fluorescence.

centrations approximately ten times as great. It was calculated from the approximate dilution in the body that the amount of riboflavin for optimum fluorescence was 0.5 mg. per kilogram and for fluorescein 5.0 mg. per kilogram of body weight. In vivo studies revealed that 0.8 mg. per kilogram of body weight of riboflavin

*Flavaxin "Niphanoid" supplied by Research Laboratory, Winthrop Chemical Co., Inc., New York, N. Y.

and 5.4 mg. per kilogram of body weight of fluorescein were desirable for satisfactory results due, perhaps, to the interference of the overlying integument and/or to the quenching effect of electrolytes of fluorescence.

Arm-to-arm riboflavin and fluorescein circulation times were compared in ten normal adults and in fifteen cardiac patients with varying degrees of congestive failure. Determinations were made at twenty-four-hour intervals (Fig. 2). The average fluorescein arm-to-arm time for the normal subjects was 18.6 seconds, the range being 13.5 to 25.6 seconds. The average riboflavin time for normal subjects was 19.1 seconds, the range being 14.5 to 26.2 seconds. In the cardiac patient the riboflavin time averaged 37.5 seconds and varied between 29.0 to 55.2 seconds. In these patients the fluorescein time averaged 33.5 seconds and varied between 19.0 and 45.2 seconds. A close correlation between riboflavin and fluorescein circulation times was present in both normal subjects and cardiac patients.

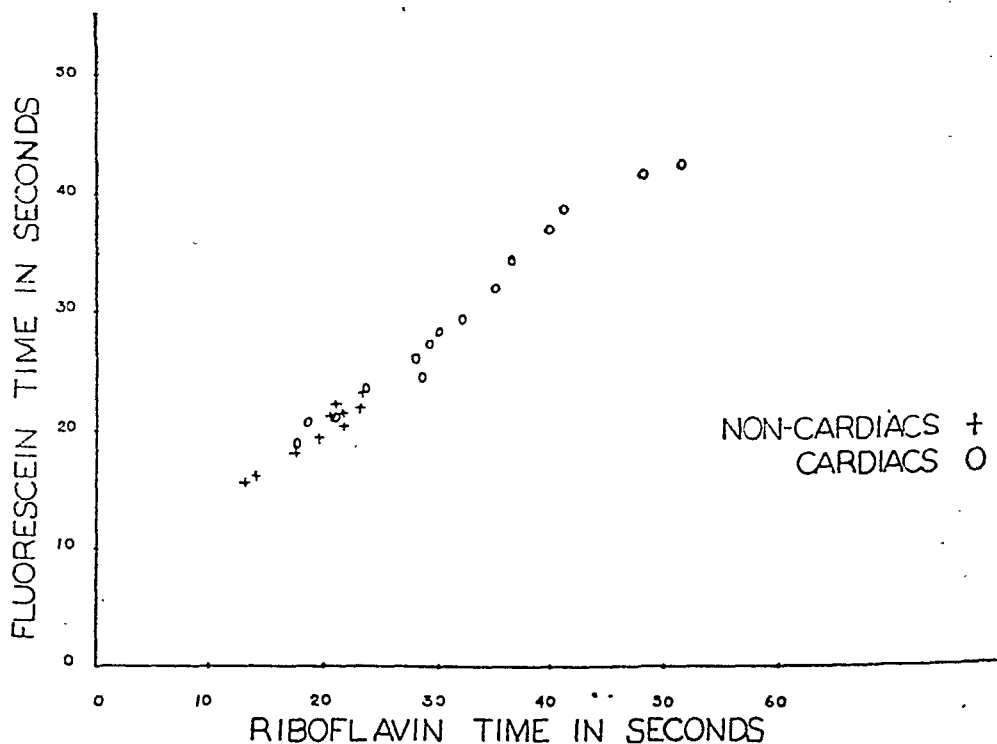


Fig. 2.—Relation between fluorescein and riboflavin times in twenty-five patients.

Arm-to-arm riboflavin times were determined in thirty-five normal individuals between the age of 14 days and 65 years (Table I). The shortest circulation times occurred in the youngest individuals. The shortest circulation time was 6.2 seconds and was encountered in the 14-day-old infant. The longest circulation time was 26.2 seconds. The average for the normal adult group was 19.1 seconds.

TABLE I. RIBOFLAVIN CIRCULATION TIMES (ARM-TO-ARM)

AGE	CARDIAC STATUS	NUMBER	CIRCULATION TIMES (SEC.)		
			MAXIMUM	MINIMUM	AVERAGE
14 Days-5.9 yr.	Normal	15	15.1	6.2	8.9
6-12.9 yr.	Normal	10	15.3	9.2	10.4
13-65 yr.	Normal	10	26.2	14.5	19.1

FRACTIONAL CIRCULATION MEASUREMENTS AND THE EFFECT OF ROOM TEMPERATURE

Circulation times through a short and long fraction of the cardiovascular system were determined. Arm-to-arm and arm-to-foot times were measured in ten normal individuals and in ten patients with marked clinical left and right ventricular congestive heart failure (Fig. 3). The average difference between

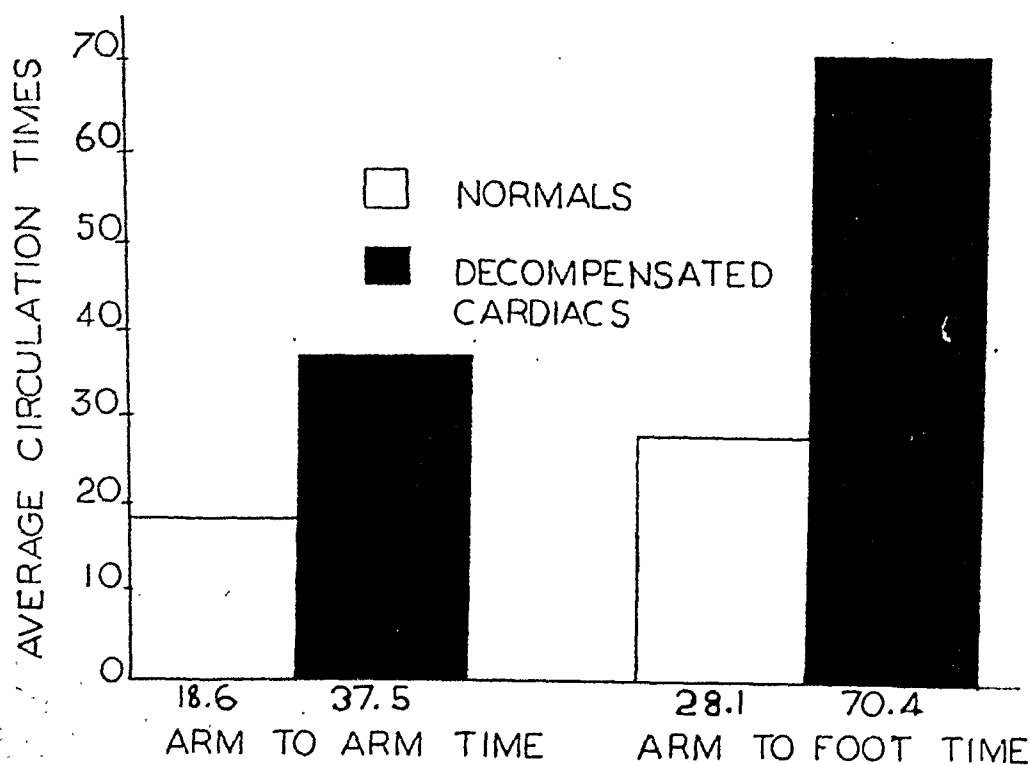


Fig. 3.—Circulation times in normal and decompensated individuals.

arm-to-arm times in normal individuals and in patients with congestive failure was 18.9 seconds, whereas the average difference between arm-to-foot times in the same groups was 42.3 seconds. These differences suggest that the arm-to-foot time is a more sensitive index of circulatory retardation than is the arm-to-arm time.

Circulation times through a systemic arterial segment were determined in normal individuals and in patients with minimal and marked congestive heart failure. The time through the arterial segment was computed by subtracting the arm-to-arm time from the arm-to-foot time (Table II). The average arterial circulation in normal subjects was 9.5 seconds and varied between 7.5 and 11.2 seconds. Among patients with minimal congestive heart failure in whom the arm-to-arm times were normal, the average arterial time was 14 seconds. A time greater than 12 seconds was suggestive of cardiac decompensation even though the arm-to-arm time was within normal limits. In severely decompensated patients, the average arterial circulation time was occasionally as long as 59 seconds.

TABLE II. CIRCULATION TIME DIFFERENCES (ARM-TO-FOOT TIME MINUS ARM-TO-ARM TIME)

	NORMAL (SEC.)	BORDERLINE (SEC.)	DECOMPENSATED CARDIAC (SEC.)
Average	9.5	14.0	32.9
Maximum	11.2	15.4	59.0
Minimum	7.5	13.8	14.9

The effect of room temperature on the appearance times of fluorescein and riboflavin was studied in ten normal and in ten decompensated cardiac patients. Patients were required to rest in a supine position for thirty minutes at a constant room temperature before determinations were made. Determinations were made at twenty-four-hour intervals first in a cold room (average 68° F.), then in a hot room (average 93° F.). Among normal individuals arm-to-arm times averaged 20 and 13 seconds in the cold and hot rooms, respectively. Among the decompensated patients the average times were 39 and 28 seconds, respectively. Arm-to-foot times in the normal group averaged 36 and 22 seconds in the cold and hot rooms, whereas the average for the decompensated patient was 79 and 50 seconds, respectively. Thus, it can be seen that room temperature has considerable effect upon arm-to-arm and arm-to-foot circulation times. Arm-to-foot times were affected to a greater degree than were arm-to-arm times. This was particularly true among the cardiac patients.

DISCUSSION

Riboflavin and fluorescein are useful in the objective determinations of fractional circulation times in man. Other objective methods, such as those employing sodium cyanide or histamine, are not suitable for fractional studies.

A suitable material for the measure of fractional times should fulfill the following requirements: It should be nontoxic and preferably not foreign to the body. The entire dose should be contained in a small amount of fluid, ideally not more than 2 cubic centimeters. It should be noninjurious and non-

painful if injected subcutaneously. It should fluoresce satisfactorily under a simple portable light source. It must be readily diffusible into tissue spaces. It should be clear and light in color. Of the substances studied, riboflavin and fluorescein most nearly fulfilled these requirements. Fluorescein* produced transient nausea in approximately 5 per cent of patients and vomiting in a smaller percentage. Burning on urination was occasionally encountered. Riboflavin was relatively free from side reactions; however, the degree of fluorescence was somewhat less than that of fluorescein. It is felt that riboflavin is the drug of choice for infants and children, since accidental subcutaneous injection is not painful and satisfactory fluorescence occurs using the wheal method. Fluorescein is probably the drug of choice for adults in whom there is no contraindication to its use.

Circulation time measurements over long segments of the cardiovascular system are often more sensitive in demonstrating the presence of left ventricular failure than are measurements made over shorter segments. A long segment of the arterial system is employed in determining the arm-to-foot circulation time. It was not uncommon for patients with congestive failure to exhibit normal arm-to-tongue times when calcium gluconate or sodium dehydrocholate were used and prolonged arm-to-foot times when riboflavin or fluorescein were employed. Such a finding occurred when minimal hypodynamic function of the left ventricle existed. Other factors such as peripheral vascular disease, polycythemia, and a cold environment might also be responsible for retardation of the circulation time. A cold environment produced prolongation of the circulation time particularly in the longer segments, that is, to the foot. It is felt that the effect of environmental temperature on the circulation is due largely to its action on the peripheral vascular system. Thus, if it is not possible to control the temperature of the room in which the test is performed, it may be preferable to record only measurements to the arm, a region which is probably affected by cold to a lesser degree.

Fractional circulation times in which the circulation time over isolated segments of the cardiovascular system are recorded are often of considerable importance in patients with altered cardiovascular dynamics. By recording the arm-to-arm and arm-to-foot time and deriving the arterial segment time, information not obtained by a single reading is found. For example, it has recently been shown that the circulation time increases with enlargement of the heart and that a prolonged time may be indicative of cardiomegaly and not of congestive failure. Determination of the arterial segment time cancels out the cardiac factor inherent in arm-to-arm and arm-to-foot times and thus gives information which is not altered by cardiac size.

The diagnostic value of fractional circulation times may be illustrated by the following: (1) The normal adult with readings recorded in a warm environment should have arm-to-arm times ranging from 15 to 25 seconds, arm-to-foot times of 25 to 35 seconds, and arterial segment times of 7 to 12 seconds. (2) With isolated right ventricular failure, the fractional times would be prolonged to the

*E. F. Kirk Co., New York, N. Y.

arm and foot, while the arterial segment time would be normal. (3) Patients with left ventricular forward failure may have normal or borderline arm-to-arm times and long arm-to-foot and arterial segment times. (4) Patients with right and left ventricular failure characteristically exhibit prolongation of all three times. (5) Patients with hyperthyroidism have all times accelerated.

The principles involved in the localization of segmental dynamics may be applied to other segments of the cardiovascular system.

SUMMARY

Riboflavin is a useful fluorescent tracer substance which is of particular value in determining the circulation times in infants and children.

Properly controlled circulation times to the foot are, under certain circumstances, a more sensitive measure of congestive heart failure than are measurements made to shorter segments of the cardiovascular system.

Fractional circulation times are useful in comparing circulatory dynamics in various regions of the body and are an aid in the diagnosis of certain cardiovascular states.

REFERENCES

1. Wiggers, C. J.: *Physiology in Health and Disease*, ed. 4, Philadelphia, 1945, Lea and Febiger, pp. 561.
2. Winternitz, M., Deutsch, J., and Brüll, Z.: A Clinically Useful Method of Measuring Blood Circulation Times by Means of Injecting Decholin, *Med. Klin.* 27:986, 1931; 28:831, 1932.
3. Weiss, S., Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *AM. HEART J.* 4:664, 1929.
4. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time With Saccharin, *Proc. Soc. Exp. Biol. & Med.* 30:651, 1933.
5. Robb, G. P., and Weiss, S.: A Method for the Measurement of Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8:650, 1933.
6. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of Circulation, *M. Clin. North America*, 26: 943, 1942.
7. Hubbard, J. P., Preston, W. N., and Ross, R. A.: The Velocity of Blood Flow in Infants and Young Children Determined by Radioactive Sodium, *J. Clin. Investigation* 21:613, 1942.
8. Nathanson, M. H., and Merliss, R.: A Method for Study of Circulation Throughout the Vascular System, *Proc. Soc. Exper. Biol. & Med.* 53:261, 1943.

THE SYNDROME OF RUPTURE OF AORTIC ROOT OR SINUS OF VALSALVA ANEURYSM INTO THE RIGHT ATRIUM

GEORGE R. HERRMANN, M.D., AND NORMAN D. SCHOFIELD, M.D.
GALVESTON, TEXAS

MODERN clinical medicine has advanced slowly but definitely by careful descriptions of symptoms and signs correlated with post-mortem findings. In a series of cases with similar anatomical lesions and very definite and clearly described ante-mortem clinical pictures, the symptoms and signs of differential diagnostic value may be grouped together in syndromes. Careful analysis of symptoms and signs of each dramatic episode which is produced by rupture of the aortic root into an adjacent great vessel or into one or another heart chamber may add to the definite clinical criteria of the condition.

As early as 1842, Hope¹ associated the clinical picture and physical phenomena of the rupture of the dilated aorta into the pulmonary artery. He cited three cases: one reported by Payne and Zeink in 1819, one reported by Willis in 1825, and one studied by himself in 1833. Scott² in 1924 and Porter³ in 1942 reviewed other cases that have been reported, and from these isolated reports and experiences with three complete cases, the syndrome of rupture of an aortic aneurysm into the pulmonary artery was delineated.

Pepper and Griffith⁴ in 1890 described the clinical symptoms and diagnostic physical signs that follow the establishment of a communication through an aortic aneurysm between the aorta and the superior vena cava. Later in 1940, this syndrome was restated by Armstrong, Coggin, and Hendrickson.⁵

The syndrome that is produced by the rupture of an aneurysm of the aorta into the conus arteriosus of the right ventricle was described by Laycock⁶ in 1860, by Lichtenberg⁷ in 1865, by Schwab and Sanders⁸ in 1931, by Tompkins⁹ in 1941, and by Harris and Shattenberg¹⁰ in 1944.

Isolated cases of rupture of an aortic sinus aneurysm into the right atrium were described by Charcot¹¹ in 1860, by Higgins¹² in 1934, and by Wright¹³ in 1937. Single cases of congenital false aneurysm and rupture through defects of the aortic septum have been recorded by T. H. Gage¹⁴ in 1863, by Abbott¹⁵ in 1919, by Micks¹⁶ in 1940, and by Shepherd, Park, and Kitchell¹⁷ in 1944. Ruptured aneurysm of the sinus of Valsalva was found four times in 3,000 autopsies by Ostrum and his associates.¹⁸ The condition was present in slightly less than one per cent of a series of 5,896 autopsies reported by Snyder and Hunter.¹⁹ While a

From the Cardiovascular Service of the Department of Medicine and the Department of Pathology, University of Texas Medical School.

Received for publication Oct. 11, 1946.

arm and foot, while the arterial segment time would be normal. (3) Patients with left ventricular forward failure may have normal or borderline arm-to-arm times and long arm-to-foot and arterial segment times. (4) Patients with right and left ventricular failure characteristically exhibit prolongation of all three times. (5) Patients with hyperthyroidism have all times accelerated.

The principles involved in the localization of segmental dynamics may be applied to other segments of the cardiovascular system.

SUMMARY

Riboflavin is a useful fluorescent tracer substance which is of particular value in determining the circulation times in infants and children.

Properly controlled circulation times to the foot are, under certain circumstances, a more sensitive measure of congestive heart failure than are measurements made to shorter segments of the cardiovascular system.

Fractional circulation times are useful in comparing circulatory dynamics in various regions of the body and are an aid in the diagnosis of certain cardiovascular states.

REFERENCES

1. Wiggers, C. J.: *Physiology in Health and Disease*, ed. 4, Philadelphia, 1945, Lea and Febiger, pp. 561.
2. Winternitz, M., Deutsch, J., and Brüll, Z.: A Clinically Useful Method of Measuring Blood Circulation Times by Means of Injecting Decholin, *Med. Klin.* 27:986, 1931; 28:831, 1932.
3. Weiss, S., Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *AM. HEART J.* 4:664, 1929.
4. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time With Saccharin, *Proc. Soc. Exp. Biol. & Med.* 30:651, 1933.
5. Robb, G. P., and Weiss, S.: A Method for the Measurement of Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8:650, 1933.
6. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of Circulation, *M. Clin. North America*, 26: 943, 1942.
7. Hubbard, J. P., Preston, W. N., and Ross, R. A.: The Velocity of Blood Flow in Infants and Young Children Determined by Radioactive Sodium, *J. Clin. Investigation* 21:613, 1942.
8. Nathanson, M. H., and Merliss, R.: A Method for Study of Circulation Throughout the Vascular System, *Proc. Soc. Exper. Biol. & Med.* 53:261, 1943.

THE SYNDROME OF RUPTURE OF AORTIC ROOT OR SINUS OF VALSALVA ANEURYSM INTO THE RIGHT ATRIUM

GEORGE R. HERRMANN, M.D., AND NORMAN D. SCHOFIELD, M.D.
GALVESTON, TEXAS

MODERN clinical medicine has advanced slowly but definitely by careful descriptions of symptoms and signs correlated with post-mortem findings. In a series of cases with similar anatomical lesions and very definite and clearly described ante-mortem clinical pictures, the symptoms and signs of differential diagnostic value may be grouped together in syndromes. Careful analysis of symptoms and signs of each dramatic episode which is produced by rupture of the aortic root into an adjacent great vessel or into one or another heart chamber may add to the definite clinical criteria of the condition.

As early as 1842, Hope¹ associated the clinical picture and physical phenomena of the rupture of the dilated aorta into the pulmonary artery. He cited three cases: one reported by Payne and Zeink in 1819, one reported by Willis in 1825, and one studied by himself in 1833. Scott² in 1924 and Porter³ in 1942 reviewed other cases that have been reported, and from these isolated reports and experiences with three complete cases, the syndrome of rupture of an aortic aneurysm into the pulmonary artery was delineated.

Pepper and Griffith⁴ in 1890 described the clinical symptoms and diagnostic physical signs that follow the establishment of a communication through an aortic aneurysm between the aorta and the superior vena cava. Later in 1940, this syndrome was restated by Armstrong, Coggin, and Hendrickson.⁵

The syndrome that is produced by the rupture of an aneurysm of the aorta into the conus arteriosus of the right ventricle was described by Laycock⁶ in 1860, by Lichtenberg⁷ in 1865, by Schwab and Sanders⁸ in 1931, by Tompkins⁹ in 1941, and by Harris and Shattenberg¹⁰ in 1944.

Isolated cases of rupture of an aortic sinus aneurysm into the right atrium were described by Charcot¹¹ in 1860, by Higgins¹² in 1934, and by Wright¹³ in 1937. Single cases of congenital false aneurysm and rupture through defects of the aortic septum have been recorded by T. H. Gage¹⁴ in 1863, by Abbott¹⁵ in 1919, by Micks¹⁶ in 1940, and by Shepherd, Park, and Kitchell¹⁷ in 1944. Ruptured aneurysm of the sinus of Valsalva was found four times in 3,000 autopsies by Ostrum and his associates.¹⁸ The condition was present in slightly less than one per cent of a series of 5,896 autopsies reported by Snyder and Hunter.¹⁹ While a

From the Cardiovascular Service of the Department of Medicine and the Department of Pathology, University of Texas Medical School.

Received for publication Oct. 11, 1946.

congenital aortic septal defect presumably was the basic cause for the development of a fistula between the aorta and the right heart in some cases, the causative disease in most cases, and even in most of the cases that have taken origin from the aortic sinuses, was syphilitic aortitis and aortic aneurysm.

Aneurysms of the aorta have been found in about 0.25 per cent of all patients autopsied, and of those dead with aortic aneurysm, more than 50 per cent died of rupture, according to Kampmeier²⁰ and Brindley and Schwab.²¹ The usual sites of the rupture were into the left pleural cavity, pericardium, esophagus, right pleural cavity, vena cava, and left main bronchus. Aneurysms of the extreme aortic root and of the sinuses of Valsalva were more often syphilitic than congenital in etiology in our local series. These were more prone to result in acquired intracardiac arteriovenous communications or fistulas than were supravulvular aneurysms.

We feel that the development of a fistula from the aortic root into the right atrium, although less common, is spectacular enough, just as is rupture into the pulmonary artery or into the superior vena cava, to produce a distinctive syndrome. Besides the cavity or vessel into which the penetration occurs, the size of the fistula determines, to a large extent, the clinical picture and the length of time of survival after the accident. The added strain on the heart is usually more than the myocardium can compensate for and the sudden failure is often overwhelming and fatal. One of our patients lived for seven days while the other was under observation for about three years after the fistula developed.

The clinical and post-mortem findings in two carefully studied cases of abnormal communications between the aortic root and the right atrium will be presented. Comparison of these findings with data from the literature and from our cases of penetration from the aorta into the right ventricle, the conus arteriosus, the pulmonary artery, and into the superior vena cava constitutes the data upon which our description of the syndrome is based.

CASE 1. (*Syphilitic Aortic Aneurysm That Ruptured Into the Right Atrium*).—E. B., (No. 54757, P. M. 4339), a 35-year-old Negro butler, was admitted to the hospital on April 13, 1937. While serving at a dinner party on April 6, 1937, he had suddenly felt, in rapid succession, a shortness of breath, extreme weakness, particularly marked in the arms, and an excruciating pain in the chest. The pain began in the midsternal line on a level with the nipple and extended downward as far as the umbilicus. It was cramp-like and associated with a sense of constriction, epigastric fullness, and abdominal tension. The patient noticed that his heart began to "jump and beat fast". He had not lifted anything heavy or made any undue physical effort. He returned to his home where he remained for six days, too ill to go to the hospital. His symptoms increased in severity. Weakness was extreme and he could scarcely get his breath. He could not lie down and whenever he would drop off to sleep, he would wake up gasping. A cough began and was productive of light, clear, and thin mucoid sputum which later became dark and thick with blood. Vomiting occurred and continued for a few days accompanied by loss of appetite. Pain in the abdomen became generalized but was most severe in the umbilical region. A bloody stool was passed before hospitalization. He developed swelling of the ankles together with a general increase in edema. He noted no fever.

The patient had worked as butler and chauffeur since 1928 and previously had done heavy work as a stevedore. He had been married twice. There had been no pregnancies in either marriage. In 1923 he acquired gonorrhea and syphilis. He was given only local treatment. His blood was examined by one physician and reported negative. He had smallpox at the age of 8 years. He had no symptoms preceding the onset of his attack.

Physical Examination.—Physical examination showed a very muscular, moderately obese Negro measuring 71 inches in height, and weighing 212 pounds. He was in acute respiratory distress and was orthopneic. His face appeared swollen. The neck veins were distended and pulsated. The whole chest seemed to pulsate. The apex impulse was in the fifth intercostal space. A prolonged, intense systolic thrill was felt most intensely over the midsternum at the level of the fourth rib but could be felt in the epigastrium. Pulsation of the engorged liver was palpable. A machine type of murmur was audible over the precordium, with systolic accentuation and maximum intensity at the third and fourth costal cartilages, and transmitted to the right and downward into the epigastrium and right upper abdomen. The systolic murmur was heard widely. The diastolic murmur was somewhat different in character. It was loud, was best heard in the subaortic area, and was transmitted down the sternum to the right, with maximum intensity at the level of the fourth rib. It could also be heard in the epigastrium (Fig. 1).

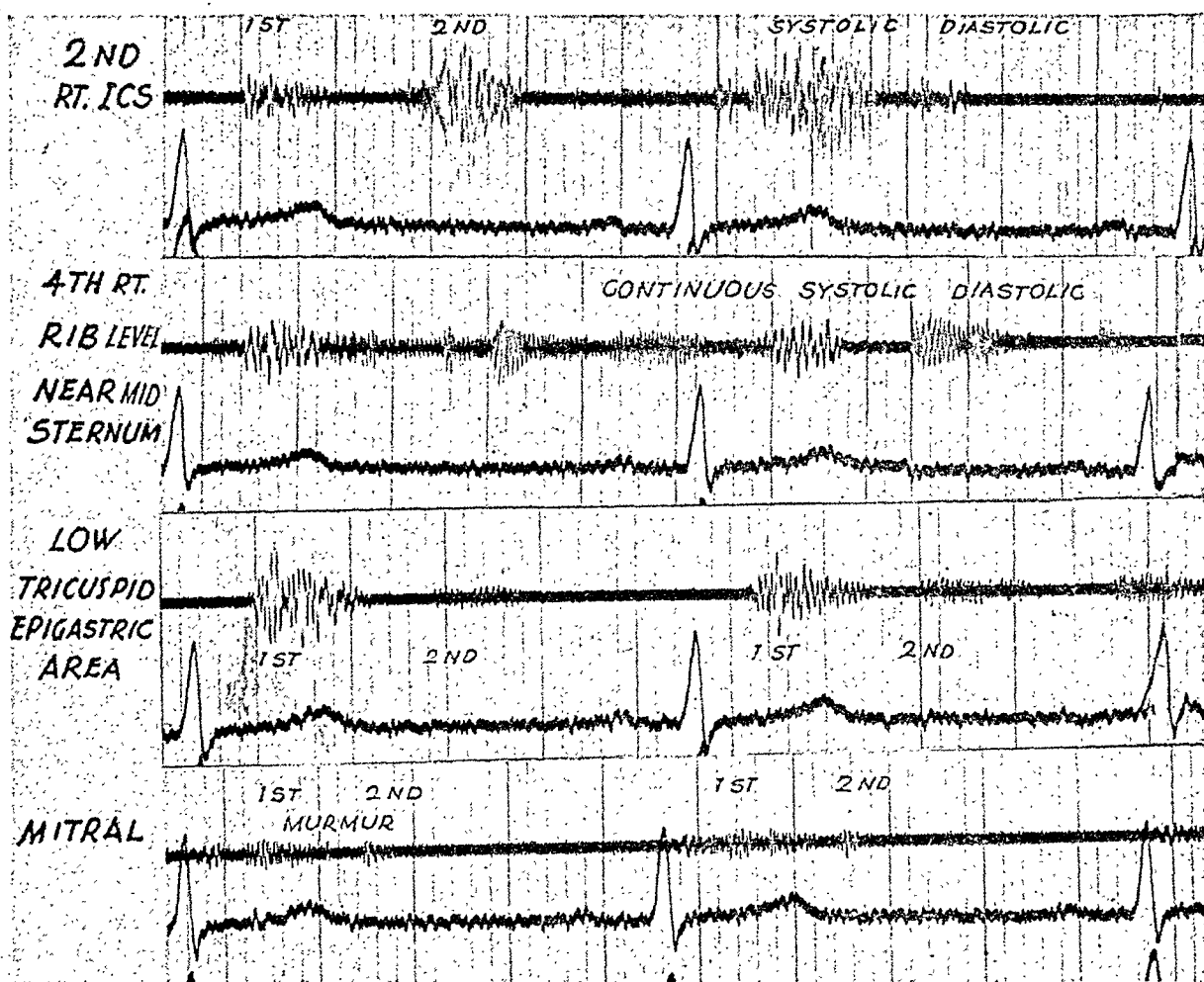


Fig. 1.—Phonocardiograms made in Case 1.

The lungs were hyperresonant and no râles were heard. The abdomen was full and rounded. Pulsations could be seen and felt in the epigastrium. The liver was engorged, and extended 5 to 6 cm. below the costal margin. Its edge was tender, smooth, and rounded. The genitalia showed an old scar on the corona. The extremities were cold and clammy. The muscles were weak, even though large and bulky. The dorsalis pedis pulses were palpable. The pressures in the brachial arteries were 120/54 on the right and 110/58 on the left; in the femorals, 144/68 on the right and 154/78 on the left. Loud pistol shot sounds were heard in both femoral arteries. The general venous pressure was considerably elevated.

An electrocardiogram made on April 13, 1937 showed right axis deviation and paroxysms of atrial tachycardia with A-V block (Fig. 2). Stethocardiograms taken April 10, 1937 showed a continuous systolic and diastolic murmur (Fig. 1). A two-meter teleroentgenogram showed a conspicuous increase in the cardiac measurements. The measurements were: transverse chest diameter, 30.5 cm.; transverse cardiac diameter, 20 cm.; length, 20 cm.; midline to left border, 12 cm.; midline to right border, 8 cm.; and aortic arch, 7 centimeters.

The blood hemoglobin was 80 per cent or 10.8 Gm. per cent, erythrocytes 4,500,000, and white blood cells 15,000; with 72 per cent neutrophils; 23 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophiles; and 1 per cent basophiles. Filament count was 88 per cent and nonfilament count, 12 per cent. Serologic tests revealed a Kolmer reaction of 2 plus and a positive Eagle test.

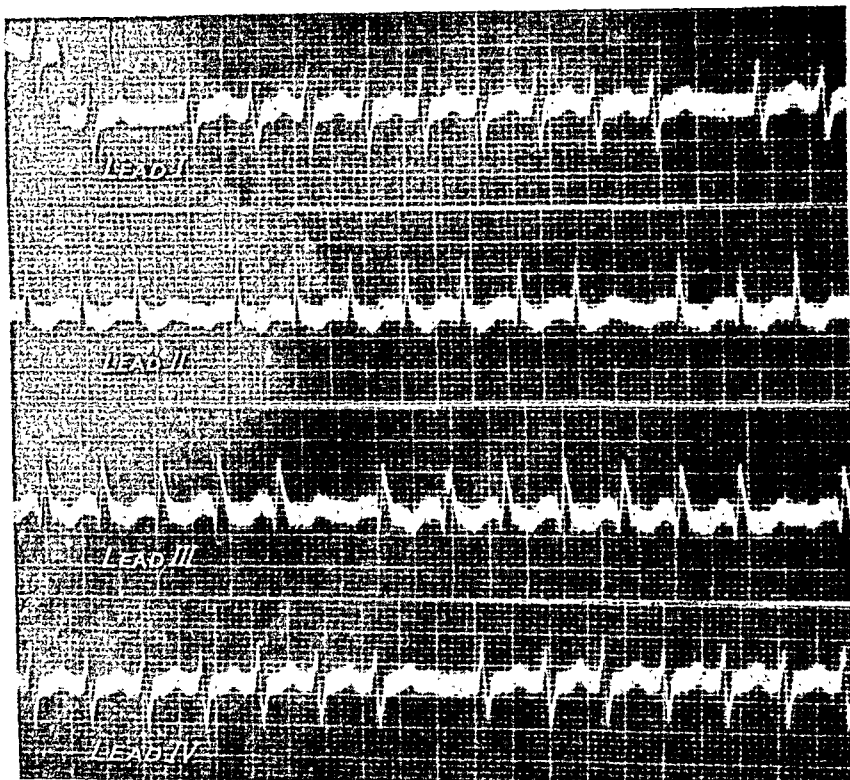
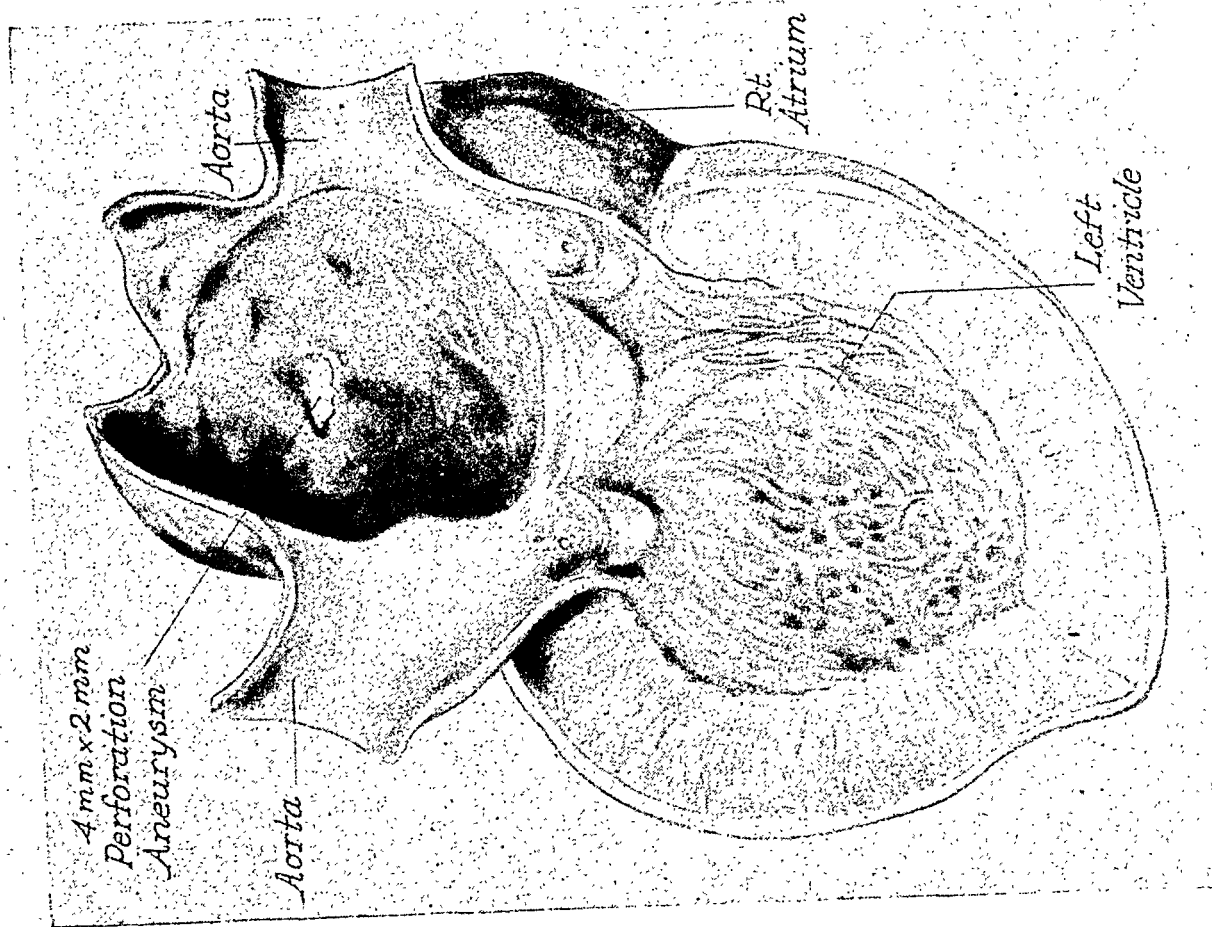


Fig. 2.—Electrocardiogram made in Case 1, showing terminal paroxysmal tachycardia with occasional A-V block.

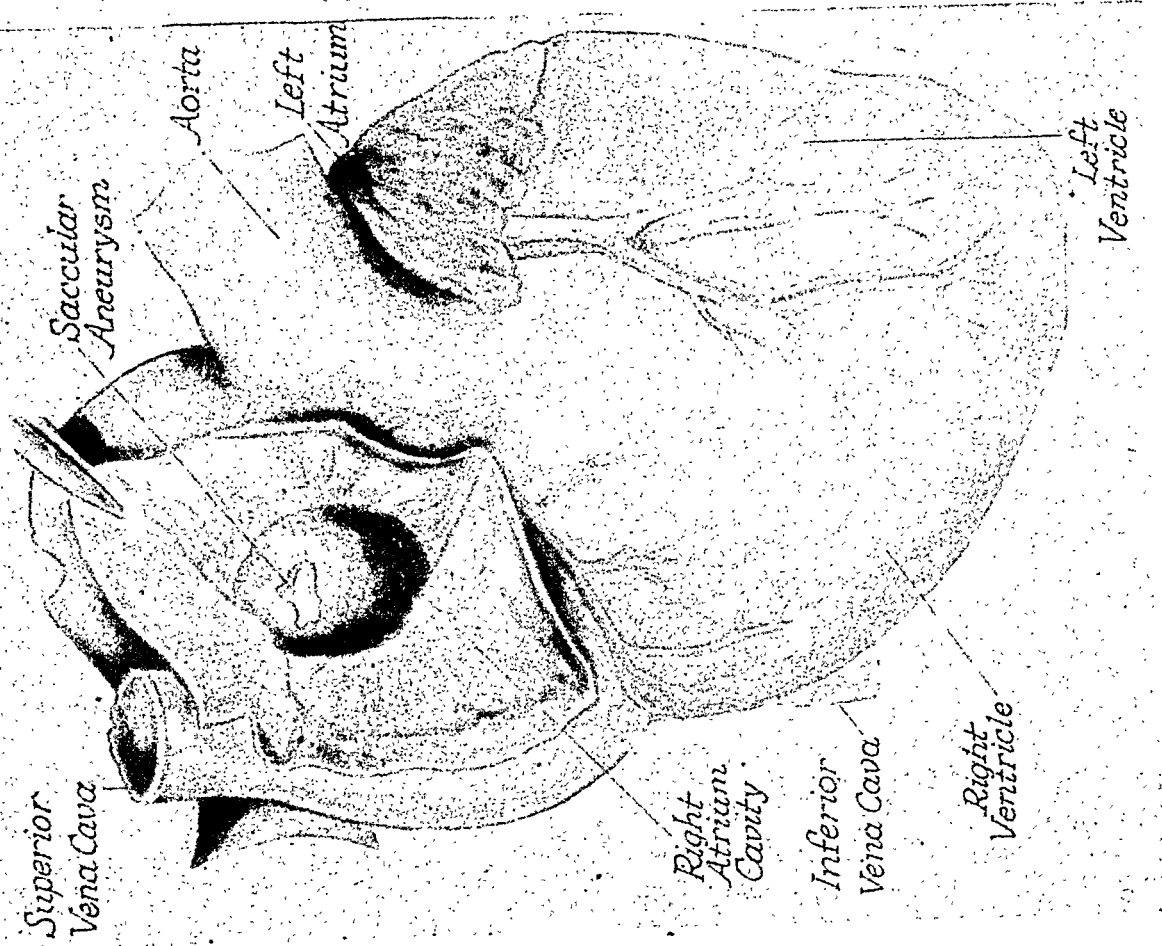
Clinical Course.—The clinical course was stormy with the patient suffering constantly from orthopnea which was unrelieved by morphine. Congestive failure was extreme with engorgement of the lungs and liver. There was hemoptysis and pulmonary edema, the patient gasping for breath. He died on April 13, 1937, seven days after the acute onset of distress. A diagnosis of an aortic root aneurysm with rupture into the right atrium was made.

Post-mortem Examination.—The body was that of an obese Negro man. There was approximately 300 c.c. of bloody fluid in the right pleural cavity and practically no fluid in the left pleural cavity. The pericardial cavity contained approximately 100 c.c. of bloodstained fluid. There were delicate adhesions between the distended right atrium and the parietal pericardium on the right.

The heart weighed 505 grams. The right atrium, the right ventricle, and the large veins leading into the right atrium were markedly distended with blood. Opening of the right atrium revealed a torn opening in the right wall medially (Fig. 3, A and B). On probing this opening



A.



B.

Fig. 3.—A, Drawing of the heart in Case 1, showing the left ventricle opened and the aorta split between the two anterior cusps, and the aortic aneurysmal bulge with the site of the ragged 4 mm. by 7 mm. rupture.

B, Drawing of the heart in Case 1, showing the right atrium opened with the irregular fistula from the aneurysmal sac into the right atrium.

it was found to lead directly into a moderate sized aneurysm of the aorta. The diameter of this tear was approximately 2 by 8 millimeters. The opening into the aorta also had the irregular edges of a recent rupture. The tricuspid ring was dilated. The right ventricle was dilated. On the right lateral aspect of the very first portion of the aorta there was an aneurysm which bulged to the right and posteriorly against the right atrium. The orifice of this aneurysm was approximately 3 cm. in diameter. The greatest inside diameter of the aneurysm was approximately 9 centimeters. There was a small amount of clotted blood adherent to the lining of the aneurysm. The coronary arteries showed some atherosclerosis, but no narrowing except at the orifices.

The liver weighed 1,830 grams. It was slightly enlarged, firm, and had a distinct, diffuse, nutmeg appearance everywhere on the external surface which was visible through the capsule. On cut section, it showed a diffuse, mottled, reddish-brown and red nutmeg pattern typical of chronic passive congestion.

Pathologic Diagnoses: (1) Acute aortic-right atrial fistula due to recent rupture; (2) syphilitic aneurysm of first portion of aorta; (3) syphilitic aortic valvulitis and aortic regurgitation; cardiac hypertrophy (505 grams) and dilatation; (4) moderate aortic and coronary atherosclerosis, moderate general atherosclerosis; (5) fibrinous pericarditis, localized over the right atrium; (6) severe passive congestion of liver, spleen, and gastrointestinal tract; (7) cortical adenoma of left adrenal gland, undifferentiated; and (8) hemorrhage into the duodenum and mesentery.

The probable cause of death was acute heart failure following rupture of an aortic aneurysm into the right atrium of the heart. The autopsy confirmed the clinical diagnosis of aneurysm of the first portion of the aorta with rupture into the right atrium, syphilitic aortitis, aortic valvulitis with regurgitation, coronary atherosclerosis, and aortic arteriosclerosis.

CASE 2 (*Congenital Aortic Defect With Dissecting Aneurysm and Rupture Into the Right Atrium*).—I. J., a 44-year-old woman, was admitted to the hospital on Jan. 20, 1941. She had been hospitalized frequently for nine pregnancies from 1925 to 1936 when cystadenomata of the ovaries were removed. She stated that all of her life, even as a child, she had had peculiar distress and a fluttering sensation in the upper part of her heart. Her eighth pregnancy was complicated by pre-eclamptic toxemia. She had a blood pressure of 188/110, albuminuria, and anemia, but normal blood chemistry findings. She had gone into shock and had been given 50 c.c. of 50 per cent glucose. This was followed by a very violent reaction with a heart rate of 136 per minute and severe precordial pain. Her blood pressure had dropped to 78/50. In 1936, after recovery from the operation, her blood pressure had been 180/120 but it gradually became lower over a period of several years.

During succeeding years there were frequent hospital admissions. The patient always complained of pain which was sudden in onset, continuous and boring in character, and located between the second and fourth rib in the intercostal margin and the sternum. The pain radiated backward to the under surface of the scapula. In 1938 her blood pressure was 130/90. In 1939 and 1940 she had frequent attacks of precordial distress which radiated to the left shoulder and down the inner side of the left arm following exertion or emotional upset. There was accompanying shortness of breath and cough.

Frequent physical examinations had shown very few diagnostic signs. The aortic second sound had been found to be loud and tambour-like in quality and a soft blowing systolic murmur had been heard in the aortic area. Six serologic studies of the blood and one of the spinal fluid between 1925 and 1941 had shown negative Wassermann, Kolmer, and Eagle reactions.

The acute attack occurred on Jan. 17, 1941, at which time she had a very severe seizure of smothering and extreme weakness while straining at stool. There was a sense of excruciating tightness and pressure in her chest. She became quite dyspneic. Three days later, on Jan. 20, 1941, she was brought to the hospital. Her dyspnea had diminished but was still present. Epigastric distress had developed and the pain in the arm was still moderately severe. The right side of her face had become swollen and her voice was quite hoarse.

Physical Examination.—Physical Examination showed orthopnea and edema of the right eye, face, and neck. There was conspicuous congestion of the jugular veins, particularly notice-

able on the right with a strong positive venous pulse. Considerable heaving activity over the precordium and to the right of the sternum was present. A long continuous thrill with systolic accentuation was felt; its maximum intensity was at the level of the fourth costosternal junction and it was transmitted slightly to the right and downward along the right border of the sternum. The apex impulse was displaced to the left and indicated marked cardiac enlargement. A loud systolic and diastolic murmur with a rough machine-like systolic accentuation was present in the subaortic area. It was most intense at the level of the fourth rib and propagated along the right sternal border to the xiphoid and into the epigastrium as far as the umbilicus (Fig. 4).

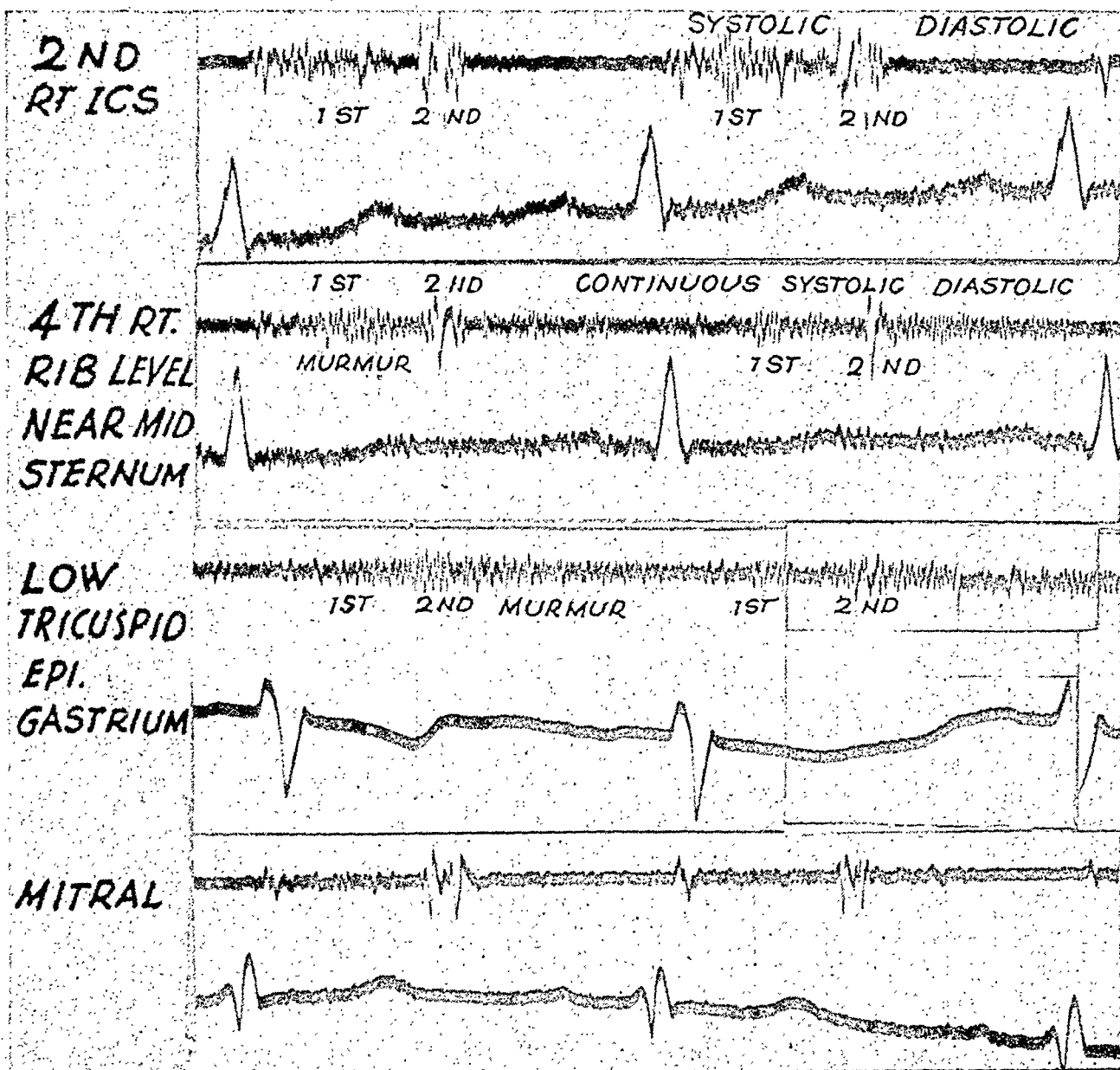


Fig. 4.—Phonocardiograms made in Case 2.

A water hammer effect was present in the carotid, brachial, and radial pulses. The blood pressure was 199/50 in both arms. Traube's pistol shot sound and Duroziez's diastolic murmur were heard in the compressed arteries. Capillary pulsations were visible in the finger tips. The venous pressure was 22.4 cm. of saline in the leg and 24 cm. in the arm. The abdomen was distended. The abdominal wall was thick and tense. The liver extended 4 cm. below the costal margin. It was smooth, slightly tender, and could be definitely felt to pulsate.

A roentgenogram showed massive increase in the cardiac shadow with an estimated increase of probably 50 per cent, with enlargement of both sides, in the right atrial as well as the left ventricular area. Kymoroentgenograms showed aortic timing quite late, suggesting the presence of aortitis.

Electrocardiogram showed left axis deviation, plus 34 degrees, and later right axis deviation and transient atrial fibrillation on Aug. 29, 1941 (Fig. 5).

The blood count showed hemoglobin, 73 per cent; erythrocytes, 3,500,000; white blood cells, 6,000; the differential count was normal. Five Kolmer and Eagle tests were negative. Blood cultures were negative. The circulation time with alphanobeline was 15 seconds, and with ether, 10 seconds.

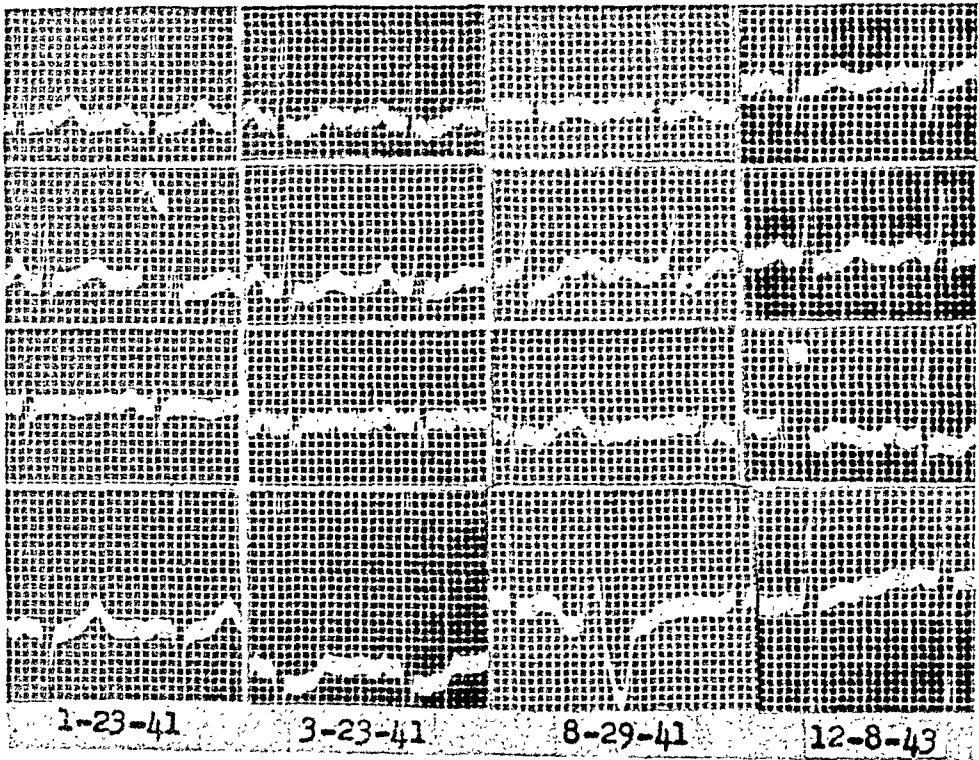


Fig. 5.—Electrocardiograms made in Case 2, showing a change in the electrical axis from left to right and atrial fibrillation on Aug. 29, 1941.

After two months in the hospital the patient was allowed to go home. Between March, 1941, and Jan. 17, 1944, she attended the outpatient clinic and was frequently admitted to the hospital for periods of one to two months because of congestive heart failure. She required mercurial diuretics and paracentesis. She had frequent attacks of precordial pain which were relieved by nitroglycerin. Occasional sharp thoracic pain was followed by hemoptysis. She occasionally had severe abdominal pain which was relieved by magnesium sulfate. Atrial fibrillation was recorded at times in the electrocardiograms. She was quite irrational at times when in congestive failure, and during her last admission she had to be restrained. She occasionally developed acute pulmonary edema which finally caused her death three years after the sudden development of her dramatic clinical picture.

Post-Mortem Examination.—Autopsy showed a large, but emaciated, middle-aged Negro woman. The nails were cyanotic. There was pitting edema of the feet and ankles.

The right pleural cavity contained an estimated 1,500 c.c. of straw-colored fluid and the left, 700 cubic centimeters. The pericardial sac showed scattered string-like adhesions over the right atrium anteriorly.

The heart weighed 480 grams. The epicardium, except for the adhesions, was smooth and glistening. The coronary arteries showed moderate atherosclerotic changes. The right atrium presented an aneurysm of its anterior wall, 4 cm. in diameter, which communicated with the aorta through a smooth fistulous opening 6 mm. in diameter (Fig. 6, *A* and *B*). The myocardium of the right ventricle was 6 mm. in thickness, while that of the left was 17 millimeters. The myocardium was pale and soft and showed no gross signs of infarction. The valves showed no gross pathologic processes.

There was an old lower midline abdominal scar 16 cm. long. There was a recent right lower quadrant puncture from which a pale, clear fluid was oozing. The peritoneal cavity contained an estimated 2,000 c.c. of clear yellow fluid. The liver was brown, small, and finely cirrhotic. Cut section revealed a very firm parenchyma. The gall bladder was small, 5 cm. by 1 cm., and contained an estimated 5 c.c. of light brown bile. The ducts showed no dilatation or angitis.

The pathologic diagnoses were: (1) Chronic aortic-right atrial fistula probably beginning in a congenital defect of the wall of the aorta; cardiac hypertrophy (480 grams) and dilatation; congestion of the viscera. (2) Hydrothorax, ascites, and dependent edema. (3) Edema of the mucosa and extravasation of blood into the alimentary canal. (4) Cirrhosis of the liver and nephrosclerosis. (5) Cerebral edema.

The cause of death was congestive heart failure. The clinical diagnosis of an aortic-right atrial fistula was substantiated by the post-mortem studies. The congenital etiology had been only lightly considered because of the long history of substernal discomfort, the good obstetrical history, and the repeatedly normal serology. The dissecting aneurysm of the right atrium was an unexpected finding. The conditions found are shown in Figs. 6, *A* and *B*.

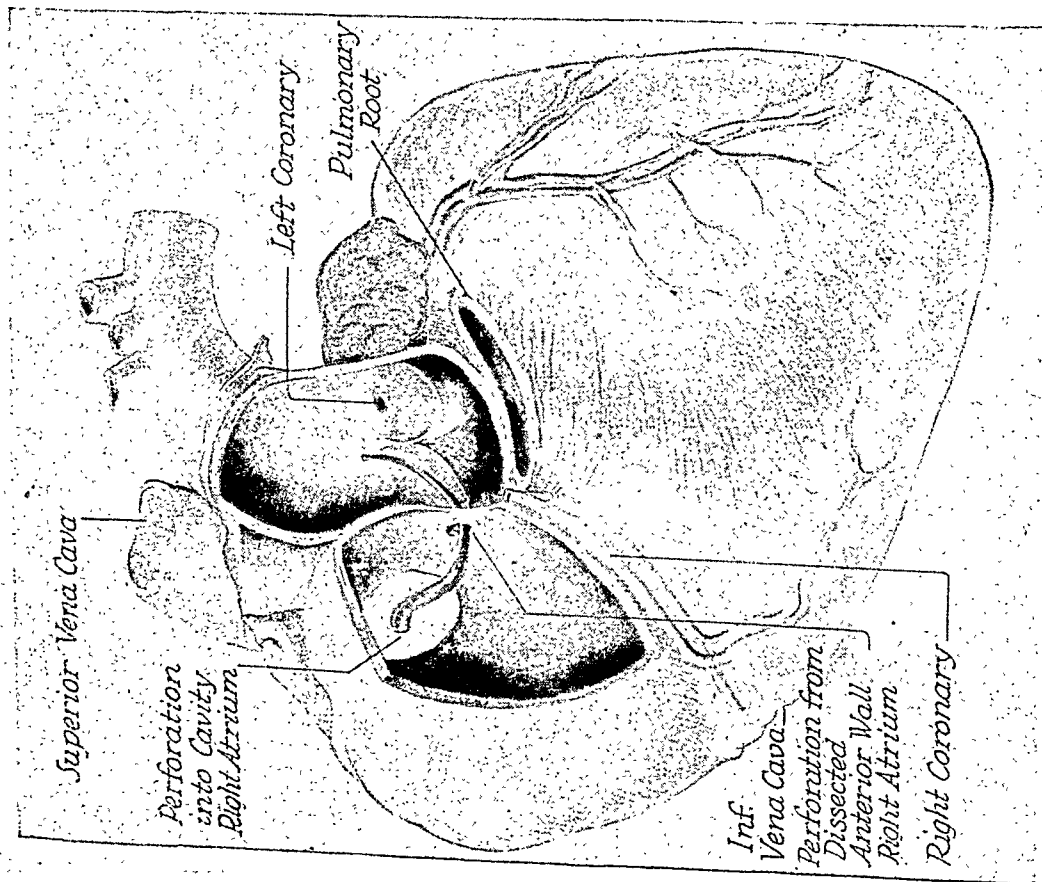
DISCUSSION

Ruptures of an aortic root aneurysm or aortic sinus aneurysm into the right atrium, right ventricle, conus arteriosus, pulmonary artery, or superior vena cava all present many similar dramatic symptoms and signs. The symptoms and signs, however, vary somewhat according to the size and site of the fistula. Distinctive characteristics develop according to the chamber or the vessel into which the communication has been made.

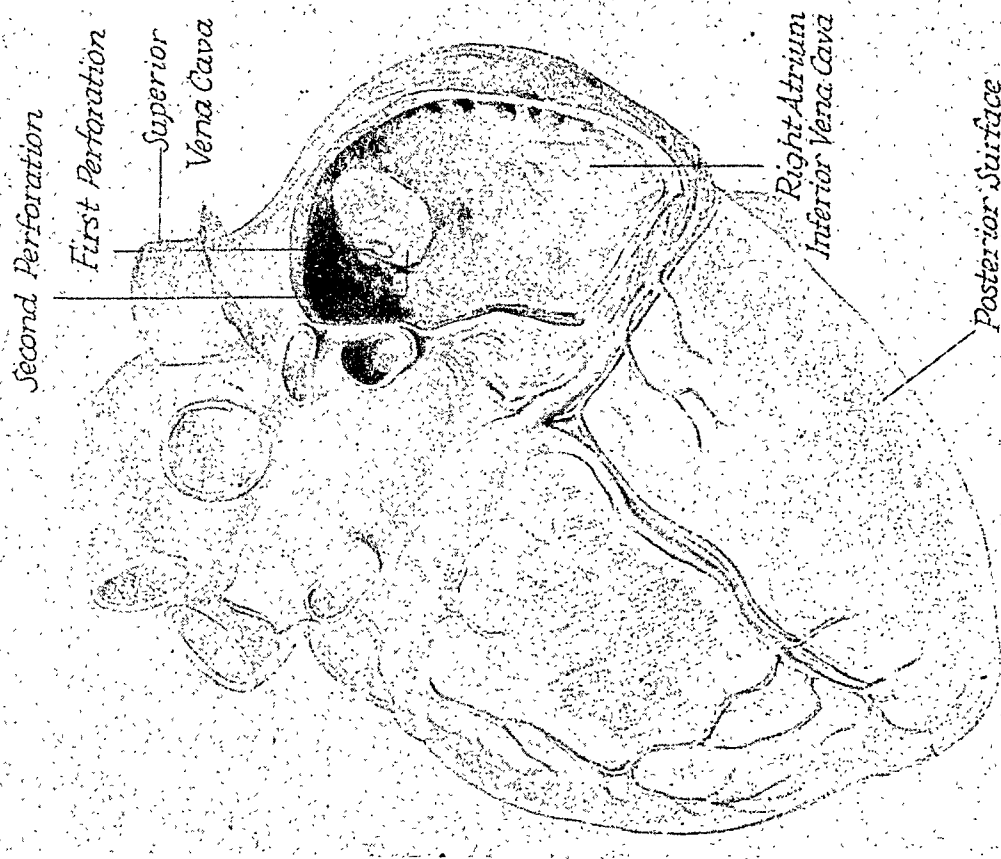
General symptoms such as premonitory boring, aching, aortic root pain, or substernal burning sensation are commonly produced by all progressing aortic root aneurysms, whether congenital, syphilitic, arteriosclerotic, or mycotic in etiology.

In the acute stage, extreme dyspnea may obscure other symptoms, but collapse, shock, exhaustion, and weakness may inaugurate the attack. Dyspnea is more severe when the fistulous tract from the aortic root leads directly into the pulmonary artery, conus arteriosus, right ventricle, or right atrium, than when the penetration is into the superior vena cava. Aortic root aneurysmal pressure may partially or even completely obstruct the pulmonary artery and produce temporary or constant pulmonary stenosis before penetration takes place and thus give premonitory symptoms and signs.

When the A-V fistula is between the aorta and pulmonary artery, the thrill and murmur are primarily systolic and are demonstrated most intensely with the patient sitting up, leaning forward, and holding his breath after forced exhalation. The pulmonic second sound is somewhat accentuated in all intra-



A.



B.

Fig. 6.—A, Drawing of the heart in Case 2, showing the anterior wall of the aorta and the right atrium cut away to demonstrate the defect in the right aortic wall. This extends from just above the right anterior aortic cusp, as shown by the curved needle, into the separated layers of the anterior wall of the right atrium. The dissecting aneurysm of the atrium communicated with the right atrial cavity posteriorly through the large oval clear window at the eye-end of the curved surgical needle.

B, Drawing of the heart in Case 2, showing the posterior aspect with the wall cut away to demonstrate the cavity of the right atrium with the large oval window from the dissecting atrial intramural aneurysm.

cardiac A-V communications, but is palpable and most strikingly augmented in the presence of direct penetration of the pulmonary artery. Dilatation of the pulmonary ring adds a high-pitched diastolic element. Dilatation and excessive pulsation of the pulmonary artery may be demonstrated and aneurysms may or may not be visualized.

The pulmonary conus arteriosus becomes much more prominent when the communication is directly into the conus, and secondarily so in penetration into the pulmonary artery from an aortic root aneurysm; especially when there has developed sufficient back pressure to produce pulmonary regurgitation as a result of dilatation. Physical and radiologic examination may reveal bulging and expansile pulsation of the part into which the aortic blood regurgitates.

Aortic root aneurysmal pressure may partially or even completely obstruct the pulmonary artery and produce temporary or constant pulmonary stenosis before penetration takes place; thus premonitory symptoms and signs should be demonstrable if looked for.

An aneurysm eroding into the right ventricle may involve the interatrial septum, the atrioventricular conduction pathway, or the intraventricular septum and the major branches of the A-V bundle. Anterior bulging and erosion from the root of the aorta may involve the coronary orifices or arteries and produce an anginal syndrome. The clinical picture of an extreme interventricular septal defect may be produced by pressure necrosis of the septum.

Acutely acquired communication between the aortic root and the right heart, in most cases, averages about three days of survival after rupture; in an exceptional case, the lesion has apparently been borne for possibly two months.

Right-sided heart failure, with elevation of the venous pressure, engorgement of the liver, and edema, develops promptly regardless of what part of the right heart or contiguous great venous system receives the blood. Cyanosis and edema of the face are not necessary or significant phenomena. Engorgement of the neck veins with a positive systolic pulsation and pulsation of an engorged liver are more common in the presence of an aortic fistula into the superior vena cava or right atrium.

The peripheral arterial phenomena of aortic regurgitation of a free type, the high pulse pressure, the water hammer carotid, brachial, and radial pulses, Traube's pistol shot sound, Duroziez's diastolic murmur and visible capillary pulsations develop in degree according to the size of the aortic defect, but are common in all such lesions.

Venous pressure is higher, the neck veins are more engorged, and the systolic pulsations are more intense when the aortic blood is directed into the superior vena cava or into the right atrium. It is less intense with penetration into the right ventricle unless this simultaneously produces insufficiency of the tricuspid ring.

The purring systolic and diastolic thrill with maximum intensity in the systolic phase is present in all cases and localized according to the position of the lesion, but modified by the extent of the false aneurysms or the fistulous tract. Localization at the point of maximum intensity of the murmurs, 1 to 3 cm. to the left in the third intercostal space suggests penetration into the conus arteriosus

or into the main pulmonary artery. Extremely loud accentuation of the pulmonary second sound usually develops.

In aortic-right atrial fistulas, there is a long, harsh, rough, continuous murmur with its point of maximum intensity at the fourth left costal cartilage in the mid-sternum and propagated along the right sternum border and usually to the right of the sternum. This sign suggests penetration into the right atrium or right ventricle.

If the fistula ends in the right atrium, and an aortic-right atrial communication has been established, the diastolic phase of the murmur becomes longer and is transmitted much further down the right border of the sternum through the inferior vena cava to the epigastrium and into the liver which pulsates. This murmur is often heard best and seems very close to the ear when the patient is lying on the right side. The aortic second sound usually persists and may often be clearly heard, while the pulmonary second sound is unusually accentuated. Palpation reveals a continuous thrill and exaggerated pulsation very near the sternum in the third and fourth intercostal spaces.

The right atrium and inferior vena cava are usually more greatly dilated when the blood stream is directed into them and produce dullness and extension of their shadows to the right of the sternum. Atrial mechanism disorders such as paroxysmal tachycardia or fibrillation are precipitated. If the fistula is of significant grade, the right ventricle will promptly be called upon to carry an extra load. The cardiac outline is globular and not of the aortic type in spite of peripheral manifestations of aortic regurgitation. The right ventricle is subjected to considerably more pressure change and there is a tendency to further development of the right axis deviation when regurgitation is into the right heart.

The symptoms and signs of an arteriovenous fistula between the great vessels or into the chambers of the heart are quite similar. However, a differential diagnosis of the anatomic localization is usually possible. The anatomic relations and the direction and fate of the shunted blood mass must be taken into careful consideration and the abnormal circulatory dynamics visualized.

An acquired communication has an abrupt dramatic onset, while a congenital fistula presents symptoms only as complications develop.

The syndrome of aortic-right atrial fistulae is thus delineated: (1) Smothering, tightness, and fullness in the chest and right upper abdomen are significant symptoms. Cyanosis is not in evidence. Râles and pulmonary edema develop late. (2) The liver rapidly becomes engorged and acutely painful and pulsates. (3) The characteristic rough, to-and-fro thrill and the machine-like murmur with systolic accentuation has its area of maximum intensity very close to the midsternal region. The diastolic murmur is loudest when the patient is in the right lateral position. The long diastolic murmur is propagated best along the right border of the sternum. Both murmurs, but especially the diastolic, are transmitted conspicuously down the inferior vena cava to the liver and to the umbilicus. These peripheral phenomena in the inferior vena cava are characteristic. (4) The right border of cardiac dullness extends considerably to the right. The axis of the heart is transverse with the shadow bulging conspicuously to the right. The whole heart is enlarged, but the silhouette is more globular in con-

tour. (5) Paroxysms of atrial tachycardia and atrial fibrillation are common. The right axis deviation usually develops as the right ventricle overcomes the strain of the high pressure overfilling through the shunt. (6) The peripheral arteriolar phenomena are similar to those of aortic regurgitation, patent ductus arteriosus, or any of the acquired shunts from the aortic root to the other chambers of the heart, the pulmonary aorta, or the superior vena cava.

REFERENCES

1. Hope, James: A Treatise on Diseases of the Heart and Great Vessels; first American edition from third British edition, Philadelphia, 1842, Lea & Febiger, pp. 439-444.
2. Scott, R. W.: Aortic Aneurysm Rupturing in the Pulmonary Artery, *J.A.M.A.* 82:1417, 1924.
3. Porter, W. B.: The Syndrome of Rupture of an Aortic Aneurysm Into the Pulmonary Artery, *AM. HEART J.* 23:468, 1944.
4. Pepper, W., and Griffith, J. P.: Varicose Aneurysm of the Aorta and Superior Vena Cava, *Am. J. M. Sc.* 100:329, 1890.
5. Armstrong, E. L., Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax, A Review of the Literature With a Report of Two Cases, *Arch. Int. Med.* 58:298, 1939.
6. Laycock, T.: Aneurysm of Aorta Opening Into Sinus Arteriosus of the Right Ventricle, *Edinburgh M. J.* 5:30, 1860.
7. Lichtenburg, I.: Aneurysm of Aorta Rupturing Into the Right Ventricle, *Tr. Path. Soc. London* 16:96, 1865.
8. Schwab, E. H., and Sanders, C. B.: Aortic Aneurysm Rupturing Into the Conus Arteriosus of the Right Ventricle, *Am. J. M. Sc.* 182:208, 1931.
9. Tompkins, R. D.: Aneurysm of the Left Aortic Sinus of Valsalva With Rupture Into the Right Ventricle (Intra-vitam Diagnosis), *M. Bull. Vet. Admin.* 18:173, 1941.
10. Harris, W. H., Jr., and Shattenberg, A. J.: Aneurysm of Aorta Rupturing Into the Right Ventricle, *Ann. Int. Med.* 20:961, 1944.
11. Charcot, J. M., (quoted by B. Dahlen): Aorta Aneurysma mit Durchbruch Im Linker Vorhof, *Ztschr. f. klin. Med.* 63:163, 1907.
12. Higgins, A. R.: Aneurysm of Sinus of Valsalva With Rupture Into the Right Auricle and Death, *U. S. Nav. M. Bull.* 32:47, 1934.
13. Wright, R. B.: Aneurysm of Sinus of Valsalva With Rupture Into the Right Auricle, *Arch. Path.* 23:679, 1937.
14. Gage, T. H.: Interventricular Opening in a Man of Robust Health, Aneurysm at the Origin of the Aorta Projecting and Finally Bursting Into the Cavity of the Right Ventricle, *Boston M. and S. J.* 69:273, 1863.
15. Abbott, M. E.: Clinical and Developmental Study of Ruptured Aneurysm of Right Anterior Aortic Sinus of Valsalva, *Osler Anniversary Volume 1*, 899, 1919, New York, 1919, Paul B. Hoeber, Inc.
16. Micks, R. H.: Congenital Aneurysms of All Three Sinuses of Valsalva, *Brit. Heart J.* 4:63, 1940.
17. Shepherd, S. G., Park, T. R., and Kitchell, J. R.: A Case of Aorto-Pulmonary Communication Incident to a Congenital Aortic Septal Defect, Discussion of Embryologic Changes Involved, *AM. HEART J.* 27:733, 1944.
18. Ostrum, H. W., Robinson, B. D., Nichols, C. F., and Widmann, B. P.: Aneurysm of the Aortic Sinuses of Valsalva, *Am. J. Roentgenol.* 40:828, 1938.
19. Snyder, G. A., and Hunter, W. C.: Syphilitic Aneurysm of Left Coronary Artery With Concurrent Aneurysm of the Sinus of Valsalva and an Additional Case of Valsalva Aneurysm Alone, *Am. J. Path.* 10:757, 1934.
20. Kampmeier, R. H.: Saccular Aneurysm of the Thoracic Aorta. A Clinical Study of 633 Cases, *Ann. Int. Med.* 12:624, 1938.
21. Brindley, P., and Schwab, E. H.: Aneurysms of the Aorta With a Summary of Pathologic Findings in 100 Cases at Autopsy, *Texas State J. Med.* 25:757, 1930.

NONGANGRENOUS FROSTBITE OF THE FEET

LIEUTENANT COLONEL DELAVAN V. HOLMAN AND MAJOR MILA PIERCE
MEDICAL CORPS, ARMY OF THE UNITED STATES

TISSUE damage from cold is by no means rare in temperate and arctic latitudes, especially among those exposed by reason of occupation.¹ War enormously increases the number of people so exposed. Resulting casualties have been numerous and have contributed to the tactical situation in the famous Napoleonic expedition to Moscow in World War I,² and in the recent conflict.³⁻⁸

Nomenclature of the clinical syndromes observed has included frostbite, trench foot, shelter foot, and immersion foot, to mention a few of the more common terms. The mechanism of production, pathologic physiology, morbid anatomy, and essentials of treatment have been summarized well by Wright and Allen.¹⁰ Except for a variety of immersion foot seen in tropical waters,^{5b} cold has been a common denominator in these variously named disorders; in our opinion their essential similarity, and not their relatively superficial differences, should be emphasized. For this purpose, the more inclusive term frostbite seems the best available term.*

The pathology of frostbite and burn have much in common, and a similar classification has been advocated by Webster, Woolhouse, and Johnston⁷ and by Wright and Allen¹⁰ as follows:

First degree—Minimum lesion involving the outer layers of skin and recoverable without tissue death (blistering or peeling).

Second degree—Damage to superficial layers of skin severe enough to produce desquamation only.

Third degree—Death to deeper skin layers and some subcutaneous tissues, sometimes involving loss of nails, tips of toes.

Fourth degree—Gangrene with loss of an extremity or notable portion thereof.

Judging from our experience in the European Theater of Operations, actual death of tissues can be a small part of the picture. Large numbers of soldiers with no more than second degree frostbite were completely disabled because of

Received for publication August 8, 1946.

*In the European Theater of Operation, through command usage, trench foot came to be applied specifically to casualties incurred by infraction of foot discipline and, in that sense, analogous to self-inflicted wounds. Casualties so labeled were not eligible for the Purple Heart Award, although foot discipline was sometimes unsatisfactory through no fault of the individual soldier. Frostbite, on the other hand, was employed for injuries acquired despite prophylaxis which was considered adequate by forward echelons. This was an added source of confusion to nomenclature.

painful, tender, vasospastic* feet. Conversely, it was noted that when there was gangrene, circulation in adjacent viable portions was usually good.

It was not clear whether death of tissues and troublesome vasospasm bore a constant relationship to one another, or whether any of the intrinsic or extrinsic factors known to favor frostbite might contribute more to development of one or the other manifestation. It was, therefore, decided to study a sample 200 casualties of frostbite, data from whom is the subject of this report.

METHODS

The work was done in the 81st General Hospital, located in the Communication Zone, during the winter of 1944-1945. The hospital was well behind combat areas and casualties were received after passing through a battalion aid station, and generally one or more other installations, in the chain of medical evacuation. They arrived on litters by hospital train and were retained for definitive treatment; that is, until fit for duty or clearly disabled for longer than the period allowed by current evacuation policies of the Theater Surgeon. There was a policy of one hundred twenty days in force during the period of this study.

The intervals between arrival of the patients in a battalion aid station and admission to general hospital varied from one to forty-five days. A majority, 139 (69.5 per cent), were received in less than two weeks. Care en route was consistent in essentials. All patients had been evacuated by litter and kept off their feet. The feet had generally been exposed to air and no other cooling device attempted. Since there was no central heating, and it was winter, this was probably adequate in most instances. Tetanus antitoxin, sulfonamide, and penicillin had been given in many, but not in all cases. There were no instances of noteworthy infection in this group. Only one patient had sympathetic block by paravertebral injections prior to reception.

The patients chosen for study were taken consecutively as they arrived at the hospital, unselected beyond chance factors that guided them to this particular installation instead of to any one of many others operating similarly.

The group represented nearly all branches of combat troops, including vehicle drivers, cooks, and radio operators. There were no service units represented. Both ground and airborne troops were included, but most of the men were infantry riflemen.

A special history and physical examination form was devised to guide, coordinate, and standardize the observations and procedures of treatment in the various wards. The following data were made available by the cooperation, group discussions, and consultations among the several members of the medical staff concerned with the care of these patients.† One of us (D. V. H.) saw each patient personally several times, and at each stage of progress.

*Vasospasm is used throughout this paper, for want of a more exact term, to indicate reduced circulation, apparent clinically as significant pallor, coldness, cyanosis, or rubor. It is the exact reverse situation from vasodilatation where local circulation is increased. Both terms actually describe net circulatory results rather than the divisions and status of peripheral vessels involved. It is commonly accepted, however, that the arterial radicals play a dominant role. The reader is referred to Discussion for further comments.

†We especially appreciate the cooperation of Major Louis Appel, Major Irwin Makovsky, Captain Isidore Rossman, and Captain Norman O'Farrell.

FINDINGS

The sample group of 200 casualties was considered first as a unit. Subsequently, in an effort to uncover the possible significance of special factors, several subdivisions were analyzed separately. The subjects of the study were all healthy as far as careful physical examinations, with special attention to the cardiovascular system and routine urinalyses, could determine.

General Survey.—

Age: One hundred five (52.5 per cent) of the entire group were 18 to 21 years of age; 35 (17.5 per cent), 22 to 25 years of age; 31 (15.5 per cent), 26 to 30; and only 29 (14.5 per cent), 30 years of age or older. Thus 85 per cent were under 30 years of age and most of these were under 21 years.

Length of Service: Most of the men, 131 (65.5 per cent), had served for a period of one to three years; 55 (27.5 per cent) had served less than one year; and 14 (7 per cent) had served three years or longer.

Combat Experience: The total time each individual had spent under combat conditions is shown in Fig. 1. Forty-six (23 per cent) had had less than a week's experience prior to onset of foot complaints, and eighty-four (42 per cent) had had less than three weeks' experience. The incidence of frostbite among veterans of more than three weeks did not vary significantly during the over-all period of forty weeks represented.

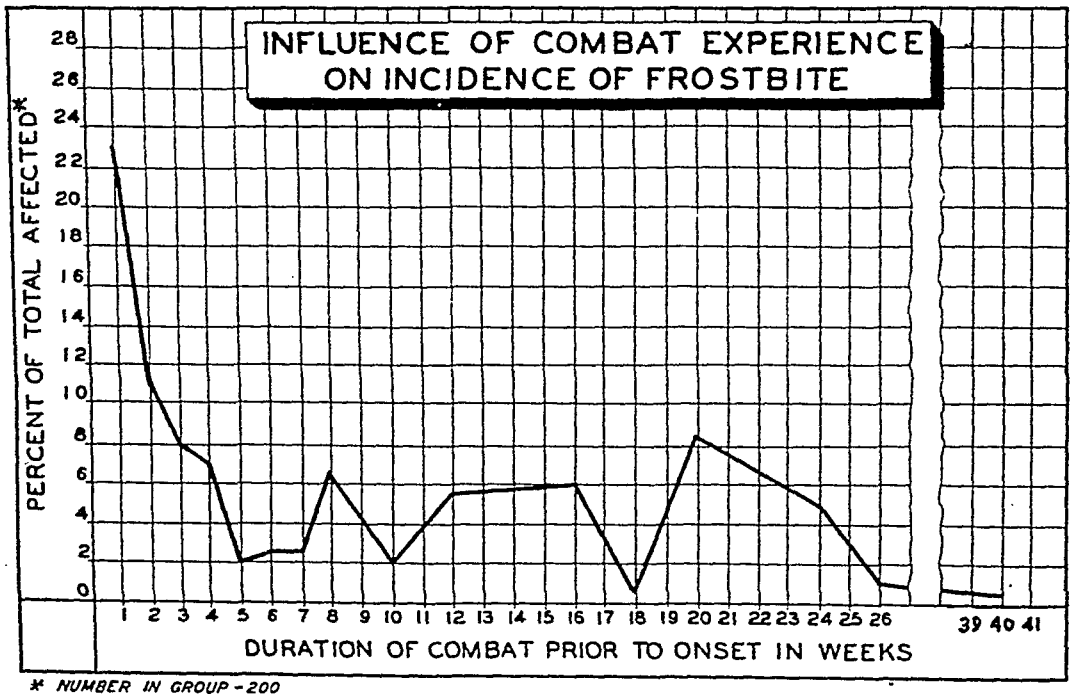


Fig. 1.—The incidence of frostbite in relation to combat experience of troops. Whereas the incidence does not vary materially among soldiers who had been in combat three weeks or longer (that is, forty weeks), it is substantially higher during the first month. In contrast, other forms of military experience and qualifications had no bearing. This seems to indicate the importance of practical field experience under combat conditions.

Rank: There were no officers among this group. One hundred seventy-four (87 per cent) were privates or privates first class, and twenty-six (13 per cent) were noncommissioned officers (corporals and sergeants), which is the standard U. S. Army distribution.

Parentage: One hundred one patients stated that their parents were American and were apparently of Northern European stock. There were 55 (27.5 per cent) whose origin was the British Isles; 10 (5 per cent), Italian; 20 (10 per cent), German; 5 (2.5 per cent), Scandinavian; 6 (3 per cent), Russian and Polish Jews; 1, Negro; and the remainder, mid-European.

Previous Frostbite: There were forty-four (22 per cent) who gave a history of known frostbite prior to the present illness.

Prefrostbite Symptoms: Pre-existing symptoms suggestive of circulatory disturbance of the lower extremities were given as shown in Table I.

TABLE I

Intermittent claudication*	14 (7.0%)
Paresthesia	17 (8.5%)
Blanching with cold	15 (7.5%)
Swelling after exposure to cold	18 (9.0%)
Acrocyanosis	21 (10.5%)
Hyperhydrosis, severe	55 (22.5%)
Vasomotor instability	15 (7.5%)
(Noteworthy circulatory phenomena such as flushing, pallor, and sweating elsewhere than in the feet)	

*In spite of the care used in history taking, the authors doubt the specificity of this symptom, which is seldom, if ever, seen with vasoconstriction alone in the absence of occlusive disease. As pointed out in the discussion, these patients were infantry soldiers and complaints of structural origin were common.

Varying degrees of anxiety neurosis, including battle fatigue, were evident in fifty-one (25.5 per cent) of the group.

Heavy use of tobacco (more than twenty cigarettes daily) was admitted by 14 per cent of the men, moderate or slight use by 73 per cent, and nonuse by 13 per cent.

Alcoholic consumption was difficult to estimate. Overindulgence ordinarily becomes evident in a soldier's military record, and there were five (2.5 per cent) who, by this evidence, were heavy drinkers. One hundred seventeen (58.5 per cent) drank "moderate amounts socially," and seventy-eight (39 per cent) were total abstainers.

Weather: The dates of onset among the group were distributed as shown in Table II.

TABLE II

October, 1944	4 (2.0%)
November, 1944	118 (59.0%)
December, 1944	64 (32.0%)
January, 1945	1 (0.5%)
Not recorded	13 (7.5%)

During this period, our combat forces were deployed widely across Northern Europe. They were exposed to a great deal of rain, moderate cold, and occasional snow. Each soldier commented upon the moisture, and 186 stated that they were forced by circumstance either to crouch in foxholes partially filled with standing water or to wade and stand in deep mud. There were ninety men who mentioned wet snow falling on unfrozen ground. The exact temperature range is not available, but it can be inferred from descriptions and what is known of climatic conditions at that season that the so-called critical* freezing point for human flesh did not prevail to any significant extent.

Etiological Influence of Weather: The total group (200) was subdivided into three subgroups according to whether the onset of manifestations occurred before November 15, between November 15 and December 15, or after December 15, 1944. The so-called intrinsic factors, the peripheral circulatory symptoms, and the neurotic stigmas were compared, but there was no noteworthy difference in the incidence among them except for hyperhydrosis and psychoneurosis. These showed parallel progressive increase with the advancing season, each commencing with an incidence of around 20 per cent and ending at approximately 40 per cent.

A subdivision analysis was made of the ninety soldiers who mentioned snowfall during the period of exposure and compared with the 110 who did not. The initial finding of these groups is listed in Columns 4 and 5, respectively (Table III). The figures were considered essentially the same in both groups. The incidence of gangrene was the same.

Duration of Exposure: Prior to onset of the symptoms of foot trouble, duration of exposure is shown in Fig. 2. There was essentially no variation in the casualty incidence between one and fourteen days' exposure. Very few patients thought they had lived under unfavorable conditions for longer than fourteen days; 24 per cent developed symptoms within forty-eight hours.

Duration of Symptoms Before Reporting on Sick Call (Battalion Aid Station): Sixty-one soldiers (30.5 per cent) reported the condition of their feet within two days of the onset of symptoms; 93 (46.5 per cent), within three days; 117 (58.5 per cent), within four days; and 170 (85 per cent) within seven days. They were all taken off their feet and evacuated as soon as they reported. There were only a few (15 per cent) who failed to report before a week.

Early Findings (Battalion Aid Station): Very often the men had not inspected their feet between the time of onset of symptoms and reporting off duty. Sometimes battle conditions intervened, but it was also common knowledge that shoes, once removed, could not be replaced on rapidly swelling feet. A list of the early signs and symptoms commonly noted, with the numbers and percentages, affected by each, is shown in Table III.

*According to Lewis,⁹ flesh freezes between -2° and 0° C. (28.4° and 32° F.), a temperature not reached until the surrounding atmosphere is -4° to -10° C. (24.8° to 14° F.), provided the skin is dry and retains its natural oils. This margin of safety is a phenomenon known as supercooling and is governed by laws of heat conductivity. Moisture, apposition of metal, and moving currents of air are especially effective in abolishing it.

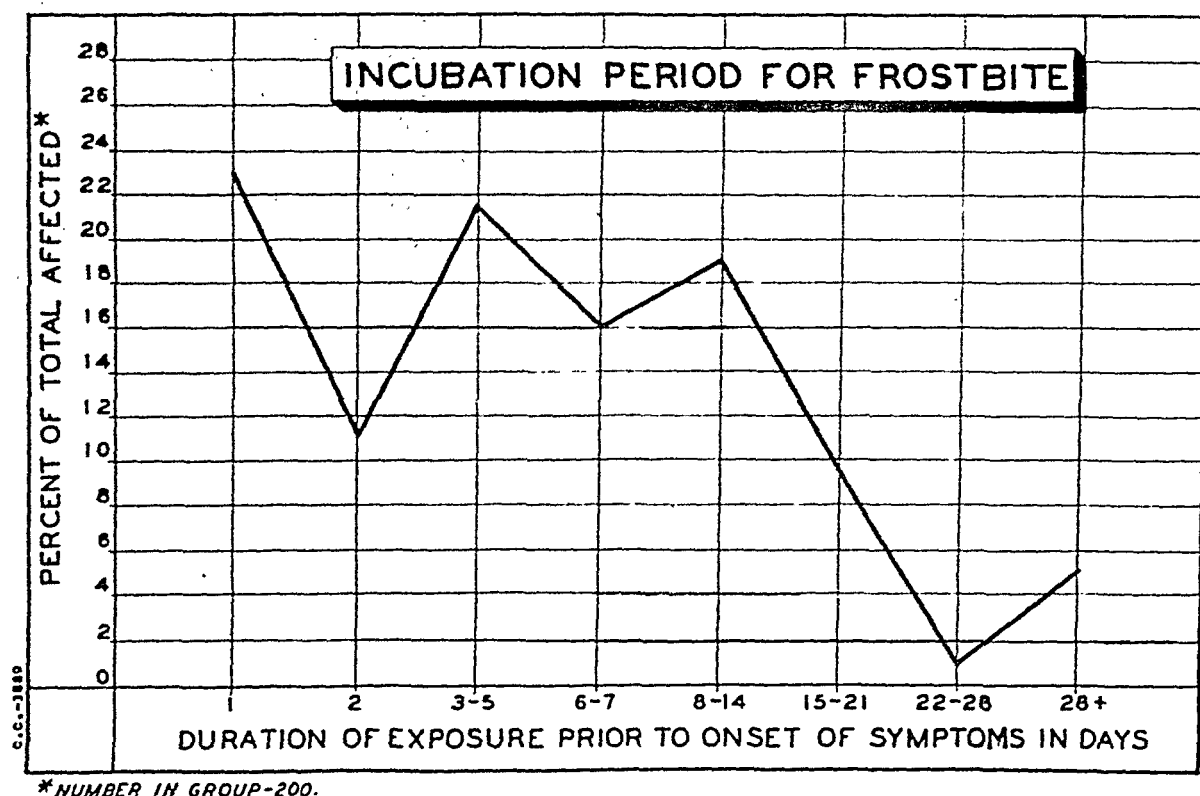


Fig. 2.—The duration of exposure prior to the onset of symptoms (that is, incubation period) is illustrated. It is apparent, other factors remaining the same, that if an individual survived exposure for two weeks or longer without developing symptoms, he had a good chance of avoiding injury. The possible significance of the length of the exposure to the clinical syndrome developed is commented upon in the text.

TABLE III. EARLY FINDINGS NOTED AT BATTALION AID STATION

PHYSICAL SIGN	ENTIRE SAMPLE (200 CASES)	SEVERELY VASOSPASTIC TREATED WITH SYMPATHETIC BLOCK (62)	LESS VASOSPASTIC (138)	EXPOSURE ASSOCIATED WITH COLDER TEMPERATURE (SNOW) (90)	EXPOSURE AT HIGHER TEMPERATURE (NO SNOW) (110)
Swelling	149 (74.5%)	30 (48.4%)	119 (86.2%)	71 (78.8%)	93 (84.0%)
Redness	30 (15.0%)	5 (8.0%)	25 (18.0%)	16 (17.7%)	15 (13.6%)
Cyanosis	52 (26.0%)	14 (22.6%)	38 (27.5%)	30 (33.3%)	26 (23.6%)
Pallor	16 (8.0%)	8 (12.9%)	8 (5.8%)	4 (4.4%)	13 (11.7%)
Heat	6 (3.0%)	2 (3.2%)	4 (2.9%)	5 (5.5%)	2 (1.8%)
Coldness	17 (8.5%)	7 (11.3%)	10 (7.2%)	8 (8.8%)	8 (7.3%)
Numbness	71 (35.5%)	30 (48.4%)	41 (29.7%)	27 (30.0%)	30 (33.6%)
Blisters	12 (6.0%)	1 (1.6%)	11 (7.8%)	5 (5.5%)	13 (11.8%)
Pain	69 (34.5%)	17 (25.8%)	52 (37.6%)	30 (33.3%)	46 (41.7%)
Gangrene	7 (3.5%)	0	7 (5.0%)	3 (3.3%)	4 (3.6%)

When medical histories were taken at the 81st General Hospital, the earliest signs of frostbite observed by the patient at the first foot inspection following the onset of symptoms were recorded. These are tabulated with the number of patients affected by each sign. In Column 1, the figures for the group (200) as a whole are listed. Columns 2 and 3 and 4 and 5, respectively, represent two special rearrangements of the data to illustrate points of interest. As described in the text, certain individuals were more vasospastic than others; 62 such persons (Column 2) are

compared with 138 controls (Column 3). It was noted that there was a tendency for patients who were more severely vasospastic when studied at the general hospital to have had an early appearance of signs (that is, coldness, numbness, pallor), whereas the controls tended toward signs of inflammation, such as swelling, pain, and blisters.

A study to show the possible etiological effect of temperature during the incubation periods of frostbite is shown in Columns 4 and 5, respectively. In Column 4, there are 90 patients, who were exposed during presumably colder weather as indicated by snowfall, for comparison with 110 patients in Column 5, who were not exposed to snow. It is apparent from a comparison of the early signs that this factor had no significant effect upon the type of frostbite developed. Other more significant factors are discussed in the text.

Findings on Admission to the 81st General Hospital.—The temperature of the feet* was considered normal bilaterally in 77 patients (38.5 per cent); one foot was normal and one was cold in 5 (2.5 per cent); both feet were cold in 67 (33.5 per cent); one foot was cold and one was hot in 8 (4 per cent); both feet were hot in 41 (20.5 per cent); and one was hot and one normal in 2 (1 per cent).

The color of the feet was normal in 47 patients (43.5 per cent). There was rubor in 98 (49 per cent); blueness in 4 (2 per cent); and pallor in 31 (15.5 per cent).

The feet of 69 (34.5 per cent) of the group had some demonstrable edema remaining when they were admitted; 32 (16 per cent) had blisters; 44 (22 per cent) had excessive hyperhydrosis, and 163 (81.5 per cent) had well-marked hyperesthesia.

Pulsations of the dorsalis pedis arteries were palpable in both feet in 151 (75.5 per cent) patients. Pulsations were palpable on one side only in 18 (9 per cent), and completely absent in 31 (15.5 per cent).†

Pulsations could be palpated in both posterior tibial arteries of all of the 200 patients.

Seven (3.5 per cent) patients had superficial areas of gangrene (third degree) on the tips of the toes or at spots subjected to shoe pressure.

TREATMENT REGIME

When each patient arrived in the general hospital, treatment was prescribed according to individual indications.

*Temperatures were estimated by the examiners by applying the backs of their hands directly to the skin. The dorsal surface of the hand, especially on the ulnar side, is more sensitive to temperature than the palmar surface. Since the temperature of the feet of so-called normal persons may vary widely and clinical estimates are necessarily inexact, whenever possible several examiners participated and groups of patients were tested concurrently. Temperature differences are more easily appreciated than absolute values.

†Since this paper was written, Silverman¹¹ has reported a study of the incidence of palpable pulsations in the dorsalis pedis and posterior tibial arteries of 1,014 healthy young soldiers, comparing the findings in Negro and white soldiers. Since our series contained only one Negro, these figures may be compared with his white group, among whom pulsations were absent in both dorsalis pedis arteries in 8.3 per cent; posterior tibials, 1 per cent; and, in one or more of the four sites, in over 13 per cent. There is no doubt in our minds that pulsations may be abolished by frostbite since they frequently appeared with treatment and acute vasodilatation induced by heat or nerve block.

In the presence of swelling, heat, and hyperemia, patients were kept in bed with their feet elevated* to a level slightly above the heart. Otherwise the bed was kept horizontal.

Trauma to injured tissues was carefully avoided and the feet were kept cool and dry. Artificial cooling was rarely necessary. The wards were Nissen huts heated by three charcoal burners spaced down the center. The heating was uneven and in winter the air at the ends of the ward and along its outer walls was always sufficiently cold if feet were uncovered.

As soon as gross edema subsided, exercise was commenced. Standard Buerger's exercises† were given, gradually at first, but rapidly increasing in duration and frequency, as tolerated. Early weight-bearing was encouraged and latrine privileges, a considerable incentive, was offered to those able to walk.

The treatment of complicating gangrene has been described elsewhere^{4,6,8} and was not a feature of this study. Gangrenous areas, if superficial, together with blisters and occasional spots of deeply exfoliating skin, need special care as protection from trauma and infection, but this usually does not greatly delay the rehabilitation program.

With exercises and symptomatic treatment, daily improvement was usual. It progressed at different rates and to varying levels, but when it halted with evidences of marked persistent vasospasm, special vasodilatory measures were added. Two such procedures were available. One was injection of lumbar sympathetic ganglia,‡ and the other, contrast whirlpool baths. As far as the present case group was concerned, sympathetic block was used selectively on those individuals with obdurate and severe peripheral vasospasm.

An active rehabilitation program was integrated carefully as a part of the treatment. As soon as weight-bearing was possible, shoes were fitted (usually several sizes larger than customarily worn by the patient) and walking was encouraged. Hikes and road marches were used to recondition the feet, and ability to tolerate these marches in winter weather formed an important criterion of progress and guided the ultimate disposition of the patient.

VASOSPASTICITY FROM FROSTBITE

As has been pointed out, vasodilation by sympathetic block was reserved for obdurate, severe cases of vasospasticity. A total of sixty-two patients were so treated one or more times. These patients were selected from the group by the degree of vasospasm which they presented, for, of course, some vasospastic reaction, as well as tissue death, was common to all. This group which was featured by marked vasospasm, was restudied and compared with the remaining 138 patients who were less vasospastic and who will be referred to as controls. The following points were of interest.

*Special wooden elevators were constructed to slip under the mattress and lift the entire leg from the hip, with the knee slightly flexed. This kept the legs comfortable and was more practicable than elevation of the foot of the bed.

†A sergeant was appointed and specially trained to supervise execution.

‡The injection technique is described in standard texts on anesthesia. The second, third, and fourth lumbar ganglia were anesthetized with 1 per cent metycaine or procaine unilaterally or bilaterally, as required.

Age: Of the special group, 58 per cent were under 21 years of age, as compared with 34 per cent of the control group.

Combat Experience: The special group tended to have had less combat experience than the controls: 42 per cent as compared with 30 per cent, respectively.

Rank: There was no significant difference in military rank or assignment.

Duration of Exposure: Severely vasospastic feet tended to have had longer periods of exposure before symptoms were recognized. This was especially noteworthy among those who were exposed less than forty-eight hours before the onset of symptoms; the figures were 11 per cent as compared with 29 per cent for the control group.

Weather: Weather conditions during the period of exposure were not different in the two groups so far as could be learned by studying the incidence of snowfall and the dates of onset of frostbite.

The intervals between onset and evacuation, that is, cessation of weight-bearing, were likewise similar.

Past History: The incidence of earlier frostbite, as well as the incidence of pre-existing peripheral circulatory difficulties and anxiety neurosis, was the same in both groups.

Early Findings (Battalion Aid Station): The figures giving the incidence of the common earliest noted findings of the severely vasospastic feet and the control group are shown in Table III, where they may be compared with each other and with figures for the entire group. Pallor, coldness, and numbness were noteworthy among the special group, whereas swelling, hyperemia, heat, blisters, and pain were more marked among the control group. All seven patients who had gangrene were among the 138 controls.

Later Findings (81st General Hospital, on Admission): Coldness of the feet was a feature in 43.5 per cent of the patients who were later treated with sympathetic blocks as compared with 29 per cent of those who were not so treated. Pallor was more notable (26 per cent as compared with 11 per cent) and pulsations of the dorsalis pedis arteries were more commonly absent (39 per cent as compared with 5 per cent). There was some ruborous discoloration of the feet in approximately 50 per cent of the patients in both the special vasospastic and control groups. Bleb formation, swelling, redness, and heat had a similar incidence among the two groups at this stage. Both groups had greater than 80 per cent incidence of hyperesthesia.

RESULTS OF TREATMENT

Of the 200 soldiers in the total group only 45 (22.5 per cent)* were returned to duty; 21 returned to combat and 24 to limited duty. One hundred twenty-five

*These figures should be considered in the light of Theater policy during the early winter, when it was decided not to congest hospitals and rehabilitation facilities with these patients. Later, the policy was reversed with consequent conservation of manpower.

(63 per cent) were returned to the United States because of persistent vasospasm, 7 (3.5 per cent) because of gangrene, and the remainder because of complicating neuropsychiatric conditions.

Of the 62 more severely vasospastic patients treated by paravertebral blocks, 4 (6.38 per cent) returned to limited duty and 58 were returned to the United States. Temporary relief of the vasospasm was obtained, but after a test period of activity in the rehabilitation unit with road marching and exposure to inclement weather, signs and symptoms recurred. There was no evidence, on the other hand, that this procedure had been harmful. Although our observations were too few and lacked sufficient control, it was our impression that the clinical course was not materially altered, one way or the other.

DISCUSSION

Of the several stages in the reaction of human flesh to cold stressed by Lewis,⁹ two main effects are important from a clinical point of view: (1) vasoconstriction and relative anoxia of local tissues and (2) actual freezing with formation of ice crystals and mechanical disruption of cellular structure.

In the group under consideration, the pathologic mechanism was that of anoxia rather than freezing. Verbal weather reports from the patients themselves indicated that although ground snow was encountered by 45 per cent of the men in the group, the temperature was above the critical freezing point for flesh. Had actual freezing of tissue occurred, the incidence and extent of gangrene could have been expected to have been much greater, for it is well known that the formation of ice crystals in tissues, once begun, usually terminates in fourth degree damage.

Anoxia causes early increase in capillary permeability, exudation, and edema, followed by intense inflammatory hyperemia, when the part is exposed to warmth. The phase of vasodilatation is generally attributed to (1) the release of histamine-like substances from damaged tissues (so-called sterile inflammation), (2) direct injury to vessel walls, or (3) vasomotor paralysis secondary to injury of peripheral nerve fibers. Very possibly all three operate.

Whichever the mechanism, as soon as vasodilatation is established, anoxia is relieved and further tissue damage interrupted, provided, of course, the process has not already advanced so far that the tissues are swollen and congested with exudates.

Histologically, injured nongangrenous tissues have shown perivascular collections of cells dominantly lymphocytes, some polymorphonuclear leucocytes, and extravasated erythrocytes, with fibrinous exudate and blockage of the finer lymphatics.¹² Arterial walls may show intimal thickening, vacuolization of muscle fibers, and, at times, thromboses. Peripheral nerves usually show considerable change, predominantly degenerative. With healing, there is collagen and fibrous deposition, especially about nerve endings and vessels, sometimes extending deeply into the muscles. Stein and Dry,¹³ studying soldier patients at a much later stage than our group, formed the opinion that "slow resolution of a chronic sterile inflammatory process with fibrosis within the tissues" is

adequate explanation for symptoms and findings. White and Warren¹⁴ reported similar findings in immersion foot.

Clinically, we observed two dominant types of nongangrenous frostbite. Judging from histories and observations recorded in battalion aid stations, both commonly developed characteristic signs very early (Table III). Although gradation of severity and admixtures of findings were more common than pure examples, certain differential signs were noted.

The first type resembled severe acrocyanosis, with dusky, mottled, engorged tissues, cool to touch and sweating profusely. Pulsations in the dorsalis pedis arteries were palpable, sometimes full or increased. In the second type, the feet were waxy pale or cadaveric in appearance, sometimes with well-demarcated lines separating affected from normal tissues, cold to touch, and with little or no swelling. Patients with this type of lesion more commonly exhibited Raynaud-like phenomena of areas of pallor succeeded by hyperemia. In early stages, this second type was likely to be considered less severe because the feet had little or no early pain, swelling, or recognizable tissue damage. Actually, patients who presented the second type of involvement proved more resistant to treatment and rehabilitation, and fewer were returned to duty in the European Theater.

As reported, the incidence of severe vasospasm was higher in the youngest age group, among those who had had the least combat experience and who had been exposed to unfavorable conditions for longer incubation periods prior to onset of symptoms. The long incubation period with long-continued ischemia and tissue anoxia of relatively mild degree compatible with continued duty may, therefore, be singled out as an operating factor. Why it caused recognizably different effects than shorter periods of more intense anoxia is not known with certainty but the factors which govern so-called reactive vasodilatation, described previously, may be concerned. If, for instance, the hyperemic phase waits upon liberation of histamine-like substances, it is clear that a relatively severe degree of anoxia is, in turn, required for those substances to be liberated by cell dissolution. Lewis has called attention to the part these substances may have in the production of pain, a symptom which is most severe during the period of hyperemia. This spontaneously occurring pain should not be confused with various paresthesias which are more a feature of other stages. Cellular death, when grossly apparent, is, of course, gangrene. In the process of separation of gangrenous from viable tissues, there is commonly a well-marked zone of sterile inflammation. If the theory under discussion is true, it would account for the fact that severe persistent vasospasm was not a feature in such cases. Similarly, it would explain the apparent import of the observed early course and why the early occurrence of hyperemia, heat, pain, and swelling gave a better prognosis. It should be pointed out, however, that the same signs, presumably more intense in degree, could presage gangrene.

As far as the individual victim of frostbite is concerned, it is important to remember that biologic variations within the so-called normal range operate also in neurovascular reflexes. Certain individuals undoubtedly respond to stimuli more readily than others, as is evident from observations on Raynaud's syndrome which can occur in anatomically healthy extremities. Vasomotor

instability, evidenced by unusual flushing, pallor, coldness, and sweating, is frequently noted in emotionally labile persons. As pointed out in the data on prefrostbite symptoms, there was a large incidence of such stigmas, although the significance of intermittent claudication is questionable. The patients were infantrymen who are notoriously susceptible to cramps and pains in the legs and feet, which are structural in origin. The differentiation of the structural and nervous origin of symptoms is, therefore, not always easy. Twenty-two per cent had earlier frostbite, which clearly suggests unusual susceptibility in the group as a whole.

We believe the incidence of anxiety psychoneuroses has significance as an indication of susceptibility and that frostbite in such individuals may result from cumulative emotional and cold stimuli. In some instances, men had been evacuated primarily for battle fatigue; in others, for frostbite. Delayed or masked anxiety states which became manifest while the patient was in the hospital were not uncommon among casualties from all causes, but in our experience they occurred more frequently in those who had frostbite. We also noted that anxiety neuroses associated with frostbite were often severe and more resistant to active neuropsychiatric treatment by the psychiatrist.

From our observations, it would be impossible to prove that occlusive arterial diseases were not a factor in the susceptibility of this group to frostbite. Ordinary clinical notation of color, temperature, and arterial pulsations were not adequate evidence in the presence of recent frostbite, and oscillometric and radiographic studies were not possible. However, careful search for evidence of vascular pathology in other parts of the system were made and were not found. There were no cases of diabetes mellitus and none had signs of thrombophlebitis. It was believed that parentage and habits (tobacco and alcohol) were very similar in this group and in comparable groups of military personnel without frostbite. And lastly, whereas such diseases are known to be important in older age groups,¹ a comparable incidence has not been reported among young persons.

Our data offered considerably less information concerning the role of extrinsic factors in frostbite (that is, foot care). These factors are generally recognized and well described elsewhere.¹⁵ The difficulties and confusion in forward echelons has been mentioned in an earlier footnote in relation to nomenclature and awarding of the Purple Heart decoration. Under these circumstances, we considered the direct evidence in response to specific questions in the taking of medical histories to be unreliable. We did analyze data which were not suspect, and, as we have pointed out, frostbite apparently tended to affect the very young soldier, in combat for the first time, in preference to the older and more experienced infantryman who was exposed to the same unfavorable climate. The factors of length and kind of military experience prior to combat, rank, available objective evidences of training, native ability, and capacity to assume responsibility proved, on the other hand, so similar to their incidence in the rest of the Army as to discount their probable importance in the etiology of frostbite. Following the same line of thought, we came increasingly to discount the influence of willful self-neglect and carelessness in the ordinary sense and developed the

more charitable point of view that involuntary situations connected with combat, in susceptible individuals, accounted for the development of frostbite in a vast majority of instances.

SUMMARY

1. An analysis of 200 frostbite casualties, observed during the fall and winter of 1944-1945 in a Communication Zone general hospital in the European Theater of Operations, is reported.

2. Marked vasospasm of the feet was the chief morbid finding in this group.

3. The etiological factors concerned in frostbite are reviewed in the light of present observations, more especially in relation to the development of vasospasm. The following conclusions are reached:

(a) Faulty foot care (extrinsic factors) is an important factor among very youthful, "green" troops unused to taking care of themselves under combat conditions. There is no apparent correlation with individual characteristics of leadership, responsibility, and military education which ordinarily predicate military assignment and rank.

(b) Some individuals are especially susceptible to frostbite (intrinsic factors). This is shown by a high incidence of one or more earlier episodes of frostbite and by the number of patients who complained of symptoms suggestive of pre-existing poor circulation. The nature of the circulatory difficulties is considered. A few of the patients may have had early unrecognized or mildly obliterative arterial lesions while sensitive vasoconstrictor reflexes may have been concerned in others. The likely role of emotional stimuli re-enforcing cold among the latter group is discussed.

4. The clinical manifestations of nongangrenous frostbite are briefly described and two broad types differentiated. It was found that conditions conducive to relatively minor grades of local tissue anoxia, sustained during long periods, were likely to produce more severe and resistant vasospasm. The likely reasons for this are discussed.

REFERENCES

1. Brahdy, L.: Frost-bite Among Employees of the City of New York, *J.A.M.A.* 104:529, 1935.
2. Mitchell, T. J., and Smith, G. M.: History of the Great War Based on Official Documents: Medical Services, Casualties and Medical Statistics of the Great War, London, 1931, His Majesty's Stat. Off., p. 88.
3. Greene, R.: Cold in Treatment of Damage Due to Cold, *Lancet*, 2:695, 1942.
4. (a) Patterson, Russell H.: Effect of Prolonged Wet and Cold on the Extremities, *Bull. U. S. Army M. Dept.* 75:62, 1944.
(b) Anderson, Fred M.: War Casualties from Prolonged Exposure to Wet and Cold, *Surg., Gynec. and Obst.* 80:1-11, 1945.
5. (a) White, J. C.: Vascular and Neurologic Lesions in Survivors of Shipwreck; Immersion-foot Syndrome Following Exposure to Cold, *New England J. Med.* 228:213, 1943.
(b) White, J. C.: Vascular and Neurologic Lesions in Survivors of Shipwreck; Painful Swollen Feet Secondary to Prolonged Dehydration and Malnutrition, *New England J. Med.* 228:241, 1943.
6. Davis, Loyal, Scarff, John E., Rogers, Neil, and Dickinson, Meredith: High Altitude Frostbite; Preliminary Report, *Surg., Gynec. and Obst.* 77:561, 1943.

7. Webster, D. R., Woolhouse, F. M., and Johnston, J. L.: Immersion Foot, *J. Bone & Joint Surg.* 24:785, 1942.
8. Ungley, C. C., and Blackwood, W.: Peripheral Vasoneuropathy After Chilling; "Immersion Foot and Immersion Hand," With a Note on Morbid Anatomy, *Lancet* 2:447, 1942.
9. Lewis, T.: Observations on Some Normal and Injurious Effects of Cold Upon the Skin and Underlying Tissues. 1. Reactions to Cold, and Injury of Normal Skin, *Brit. M. J.* 2:795, 1941.
10. Wright, I. S., and Allen, E. V.: Frostbite, Immersion Foot, and Allied Conditions, *Army Bull.* (no. 65), p. 136, 1943.
11. Silverman, Jacob J.: The Incidence of Palpable Dorsalis Pedis and Posterior Tibial Pulsations in Soldiers, *AM. HEART J.* 32:82, 1946.
12. Friedman, N. B.: The Pathology of Trench Foot, *Am. J. Path.* 21:387, 1945.
13. Stein, I. D., and Dry, T. J.: Vascular Injuries Due to Cold With Particular Reference to the Late Phase of Trench Foot, *Modern Concepts of Cardiovascular Disease*, 15: no. 9, 1946.
14. White, J. C., and Warren, S.: Causes of Pain in Feet After Prolonged Immersion in Cold Water, *War Med.* 5:6, 1944.
15. News and Comment: Trench Foot, *Bull U. S. Army M. Dept.* 4:265, 1945.

THE DIAGNOSIS OF TRICUSPID VALVE DISEASE

SALVADOR ACEVES AND RAFAEL CARRAL
MEXICO, D. F., MEXICO

THERE exists considerable divergence of opinion concerning the frequency and the diagnosis of lesions of the tricuspid valve. Opinions expressed by different authors not only have differed, but, at times, also have been diametrically opposed.¹⁻⁸ To a great extent these divergent points of view have been a reflection of the era in which the study was made.^{3,10} An example of this fact is found in *Oxford Medicine*. In this book, MacKenzie,⁹ who wrote the original chapter on the tricuspid valve, stated that organic lesions affecting this valve are rare and that in all his cardiologic experience he had found a presystolic tricuspid murmur in only three cases. On the other hand, Herrmann,⁶ writing more recently on the same subject and in the same book, stated that these lesions are found in 25 to 30 per cent of all patients with chronic rheumatic mitral disease.

This disagreement can be explained, at least partially, by the fact that most authors speak of tricuspid lesions or tricuspid stenosis or tricuspid insufficiency without specifying exactly what they mean when they make these diagnostic distinctions. Some authors speak only of stenosis when there is fusion of the valve leaflets or thickening and sclerotic changes in the valve ring, even though valvular retraction and shortening of the chordae tendineae have also produced insufficiency. Other authors limit the diagnosis of stenosis to those lesions in which actual narrowing or an infundibular conformation of the valve orifice is the only peculiarity. Others give more attention to the clinical features of insufficiency and do not take into consideration the fact that almost invariably chronic regurgitation is accompanied by a concomitant stenosis. Garvin¹¹ believes that the presence of the symptomatology of regurgitation is sufficient to justify a diagnosis of stenosis.

To avoid the difficulties of nomenclature, it would be better to adopt the general name of tricuspid disease, as do Kerr and Morrison.² Because of the clinical nature of our paper and because of the importance of the symptoms of insufficiency, we have followed this course.

When we began our clinical studies, we accepted the opinion of other workers, that tricuspid lesions were not a common finding. Our clinical and necropsy studies, however, have taught us that lesions of the tricuspid valve are more frequent than is generally thought. The purpose of this paper is to present some of the observations and impressions that have come from our study of this interesting subject.

From the National Institute of Cardiology.

Read at the Inter-American Congress of Cardiology, Mexico City, Oct. 5-12, 1946.

MATERIAL AND METHODS

From September, 1944, to July, 1946, 250 autopsies were performed at the National Institute of Cardiology. Among these 250 patients, only six had normal hearts; of the 244 patients with cardiovascular disease, 147 (60.2 per cent) had rheumatic heart disease. Of the patients with rheumatic heart disease, seventy-three (49.6 per cent) had some degree of tricuspid involvement although only forty-nine (33.33 per cent of the total rheumatic series) had the type of deformity which produced tricuspid insufficiency. In eight cases (5.44 per cent) functional tricuspid insufficiency (without lesion of the valvular endocardium) was present.

Criteria for Diagnosis of Tricuspid Lesions.—Relative stenosis was deduced from the circumference of the valve, measured at the ring where the leaflets were not fused and measured at the free edge of the leaflets where fusion existed. The absolute figure of the valvular circumference was adjusted in accordance with the weight, height, age, and constitution of the subject. In addition to the circumference of the valve, the inlet and outlet tracts of the right ventricle were considered. Generally the outlet tract (the distance from the apex of the right ventricle to the pulmonary semilunar valves) is 10 to 15 mm. longer than the inlet tract (the distance from the tricuspid ring to the apex of the right ventricle). Enlargement of the ventricle nullifies or inverts this difference. Because of these various adjustments, even with absolute figures within normal limits, a *relative* stenosis may be present. Absolute or real stenosis is quite rare and, when present, is so obvious that there can be no doubt of its presence. It is interesting to observe that tricuspid stenosis does not produce auricular hypertrophy as does mitral stenosis.

Tricuspid insufficiency was deduced in two ways: (1) from the condition of the valves—their shortening or retraction, state of the edges and the length, thickening, and fusion of the chorda tendineae; and (2) from the effects of insufficiency—enlargement of the right ventricle, dilatation of the venae cavae, especially the inferior, condition of the liver, and particularly the state of the suprahepatic veins within the parenchyma.

Even though we recommend the general term tricuspid lesions for clinical use and insist that stenosis and insufficiency are combined in most instances, we have differentiated insufficiency and stenosis on the basis of pathologic findings. We have considered as true stenosis eleven of the forty-nine cases with organic tricuspid lesion (22.44 per cent) in which narrowing predominated over insufficiency from a strictly anatomic point of view. Our basis for asserting this was the evident fusion of the valves, the funnel type of orifice, or the marked decrease in the circumference of the valve ring.

We considered as cases of pure insufficiency those in which it was evident from the condition of the valves that regurgitation existed and predominated over the stenosis which was also present. Such insufficiency was found in twenty-eight (57 per cent) of the forty-nine cases with organic tricuspid lesions. In eleven cases (24 per cent) the evidences of both insufficiency and stenosis were so marked that it was considered proper to classify these as examples of double tricuspid lesions.

We found one isolated case of tricuspid valvulitis with insufficiency in a patient with bacterial endocarditis where autopsy did not show rheumatic heart disease. This completes a total of fifty cases of tricuspid disease of clinical importance.

With the exception of this one case of bacterial endocarditis in which valve damage was limited to the tricuspid valve, all of the remaining seventy-three cases of tricuspid valvulitis showed lesions of other valves. Of the fifty cases with important tricuspid lesions, only one (2 per cent), as we have said, presented a lesion of this valve alone; one (2 per cent) had a tricuspid lesion and mitral insufficiency; three (6 per cent) had a tricuspid lesion and pure mitral stenosis. In the other cases, the tricuspid lesions were associated with lesions of other valves as follows: double mitral lesion in eighteen cases (36 per cent), mitral and aortic lesions in twenty-seven cases (54 per cent), and, in one case, already cited, lesions of the other three valves (aortic, mitral, and pulmonary).

The eight cases of functional insufficiency of the tricuspid valve were accompanied by the following lesions which explained right ventricle dilatation: in five, the tricuspid lesion was accompanied by a double mitral lesion; in two, double mitral and aortic lesions; and, in one, by double aortic lesion.

In the fifty cases diagnosed as organic tricuspid lesion, twenty-four presented pulmonary infarcts (48 per cent). Five cases presented phenomena of thrombosis; in two the thrombus was located in the body of the right auricle (both patients had pulmonary infarcts) and in three the thrombus was in the right auricular appendix (one of these patients had pulmonary infarction). In eleven cases the lesions were accompanied by different types of pericarditis.

ANALYSIS OF SIGNS AND SYMPTOMS

Age.—The average age of fifty patients with tricuspid disease was 24 years. The minimum age was 9 years and the maximum age, 69 years.

Sex.—This series of fifty patients was composed of thirty-four women (68 per cent) and sixteen men (32 per cent).

Duration.—The average duration of the disease from the appearance of symptoms until death was judged to be sixty-four months.

Accuracy of Diagnosis.—The clinical diagnosis of tricuspid disease was proved by necropsy in seventeen (34 per cent) of the fifty patients.

Dyspnea.—Dyspnea on exertion was present in almost all patients. The histories of only two patients (4 per cent) indicated that this symptom was absent. Dyspnea in the supine position was stated to be present in thirty patients (60 per cent). It was apparently not present in twelve patients (24 per cent); the symptom was doubtful in eight patients (16 per cent). In three of the thirty patients, this symptom was present toward the end of illness; in three more patients, it was stated to be present at some time during the course of illness but was not present at the time of death.

Paroxysmal dyspnea was not an outstanding finding. This symptom was absent in thirty-six patients (72 per cent) and in three patients its existence was doubtful. Six patients (12 per cent) had episodes of acute pulmonary edema. Five additional patients (10 per cent) had something approaching pulmonary edema, but the data in the histories were not sufficient to justify a positive diagnosis.

Cough.—This symptom was absent in fifteen patients (30 per cent) and present in thirty-five patients (70 per cent). Fourteen patients (28 per cent) had hemoptysis. In six of these (12 per cent) the bloody expectoration was explained by pulmonary infarction, and in two (4 per cent), by pneumonia. In only six patients (12 per cent) could the hemoptysis be related to pulmonary congestion alone.

Cyanosis.—This sign was positive in twenty-eight patients (56 per cent). In seven of these patients (14 per cent) cyanosis was quite intense, in nine (18 per cent) it was of medium intensity, and in twelve (24 per cent) it was slight.

Color of the Skin.—Pallor was present in six patients (12 per cent), ashy pallor in twenty patients (40 per cent), pallor with cyanosis in eight patients (16 per cent), pallor with slight jaundice in four patients (8 per cent), pallor with cyanosis and slight jaundice in four patients (8 per cent), and marked jaundice in one patient (2 per cent).

Venous Distention.—This sign was present in the veins of the neck in forty-two patients (84 per cent). In eighteen of these patients (36 per cent) it was marked, in fifteen (30 per cent) it was of medium degree, and in ten patients (20 per cent) it was considered to be slight. Marked edema of the face was present in only six patients.

Venous pressure in the upper limbs was determined in thirty patients, in some of whom the procedure was repeated several times. The lowest venous pressure was 40 mm. H₂O, the highest, 240 mm. H₂O, and the average, 149 mm. of water.

Circulation time was determined by the decholin method in thirty patients. The minimum was 9 seconds, the maximum, 48 seconds, and the average, 26 seconds.

Ascites of varying degree was present in twenty-four patients (48 per cent). Edema was present in forty-two patients (84 per cent). In eight patients edema was generalized; in four it involved the lower limbs and face; in three it involved only the face (there were no signs of kidney disease); and in twenty-seven (54 per cent), only the lower limbs were involved.

Venous Pulse.—This sign was present in neck veins in eighteen patients (36 per cent). In four patients with marked jugular distention the venous pulse became more apparent in the sitting position and decreased with increase of the distention of the jugular vein brought about by assuming the prone position. The segment of the vein in which the pulse could be seen extended higher in the neck in decubitus than in the sitting position. This peculiarity has been described by White in patients with cor pulmonale and observed by Rivero Carvallo²⁶ in patients with tricuspid regurgitation.

Spontaneous Liver Pain.—Liver pain of variable intensity was a constant finding. Pulsation of the liver was a less frequent finding. Nine patients (18 per cent) developed intense paroxysmal pain in the epigastrium or right hypochondrium which radiated to the posterior aspect of the thorax and, less frequently, to the shoulder. These episodes of intense pain lasted from a few hours to several days and were frequently accompanied by vomiting.

Vomiting.—The appearance of vomiting not related to digitalis intoxication was a common finding (fourteen patients, 28 per cent). Often the history of patients with this symptom indicated that the vomiting was repeated in crises upon several occasions.

The Liver.—Hepatomegaly was a constant finding in all patients. In four patients (8 per cent) the liver was palpable only 1 to 4 cm. below the costal border in the midclavicular line. In all others, the liver extended more than 5 cm., and in two patients, 16 cm. below the costal border.

There was no mention of the consistency of the liver in seventeen patients. In the remaining thirty-three patients, consistency was increased in thirty (90.9 per cent), while no increase in consistency was noticed in three (9.1 per cent). Tenderness of the liver was present in forty-seven patients (94 per cent). Pulsation of the liver was studied in twenty-one patients (42 per cent). The sign was present in sixteen and absent in five patients. The function of the liver was studied in only twelve patients. In three (25 per cent) the function of the liver was found to be normal, and in nine patients (75 per cent), functional insufficiency was found.

In these nine the bromsulfalein test (Greene technique) showed a fixation of the substance in the liver of from 70 to 90 per cent, with an average of 82 per cent (normal, 95 to 100 per cent). Ten to 30 per cent of the dye was present in the blood: the average was 18 per cent (normal, 0 to 5 per cent). In these nine patients the van den Bergh test (Jendrassik-Czike method) gave positive results. The prothrombin index was studied in five patients. In three of these the index was decreased.

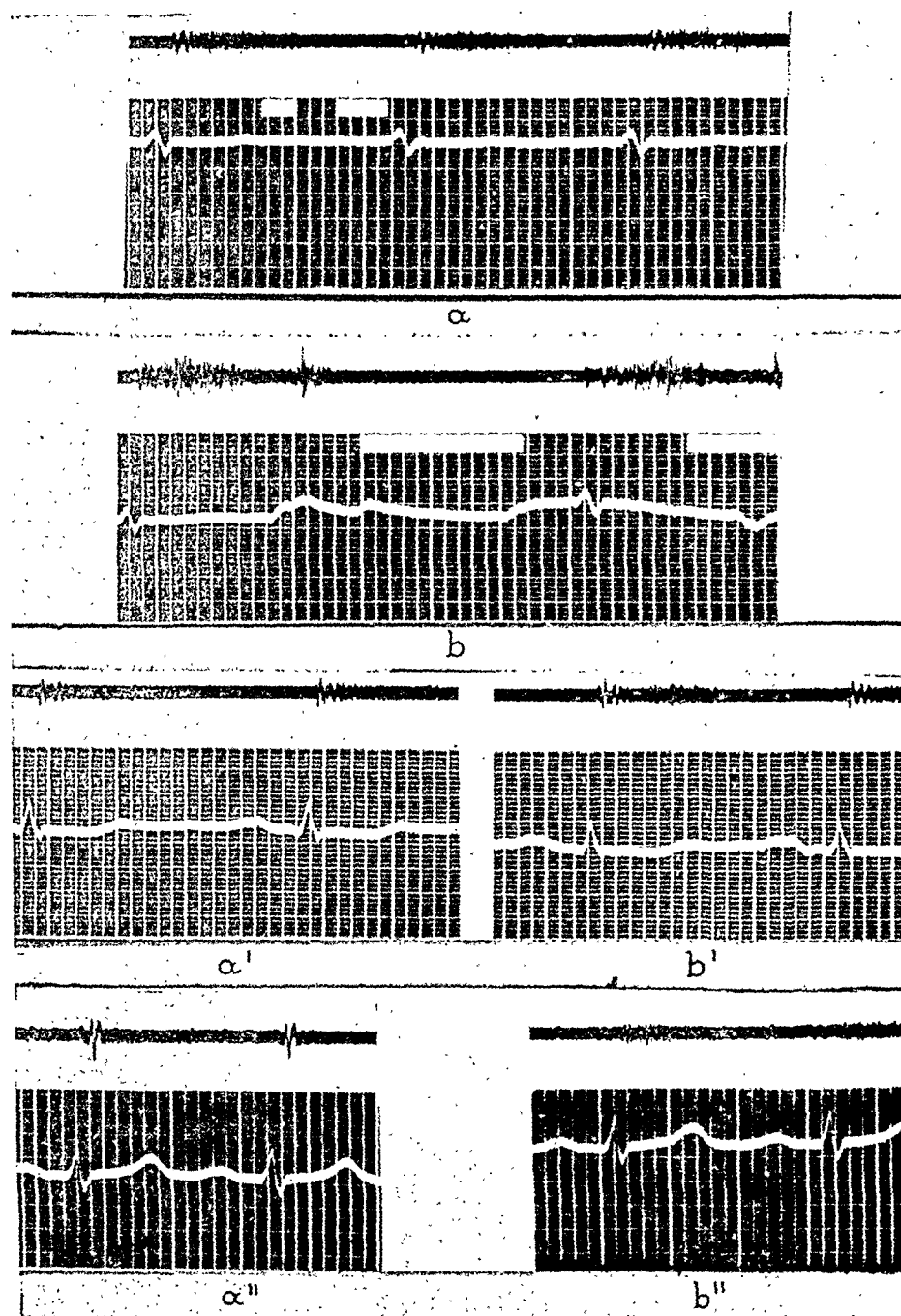


Fig. 1.—Phonocardiograms at the tricuspid area. In *a*, *a'*, and *a''*, during postexpiratory apnea; in *b*, *b'*, and *b''*, during postinspiratory apnea. Observe in *b*, *b'*, and *b''* the increase of the intensity of the systolic murmur when compared with *a*, *a'*, and *a''*.

Auscultation.—In seventeen patients (34 per cent) a tricuspid systolic murmur was identified. In eight patients the murmurs were identified by their acoustic characteristics, which differed from those of the concomitant mitral murmur. No special methods were employed.

In the other nine patients the method described by Rivero Carvallo²⁵ was used in order to identify the tricuspid origin of the murmur. This method consists in auscultation in postinspiratory and postexpiratory apnea.

Applying Levine's classification, the murmur was considered to be grade 1 in three patients, grade 2 in eight patients, grade 3 in five patients, and grade 4 in one patient. The murmur was highly pitched in all but one patient. It was more or less harsh ("*en jet de vapeur*") in all but two patients, in whom it was musical. In twelve patients the murmur was transmitted toward the hepatic area and the region contiguous to the tricuspid area. In one patient the murmur could be heard at the apex. The first sound was absent in nine patients.

In ten patients the characteristics of the murmur were studied successively in postinspiratory and postexpiratory apnea (Fig. 1). In nine of these (90 per cent), increase in the intensity of the murmur over the tricuspid focus and an increase in the area over which it was transmitted occurred during postinspiratory apnea (Fig. 1). The murmur also became high pitched.

Electrocardiographic Findings.—Electrocardiograms were studied in forty-four patients. Auricular fibrillation was present in thirteen patients (29.5 per cent).

In thirty-one patients who did not have auricular fibrillation, the features of the P wave were analyzed in the three standard leads, the three limb potentials, and the six precordial leads (Wilson's method). The P wave was abnormal in every instance, being notched in twenty-seven patients and slurred in four.

The duration of the P wave was at least 0.10 second in twenty-five patients (80.5 per cent) and less than 0.10 second in six (19.5 per cent). The duration in the patient with an isolated tricuspid lesion was 0.08 second.

The mean manifest axis of P (\hat{A}_P) fell between +60 and +90 degrees (isoelectric, diphasic, or negative P in V_L , positive in V_F and standard leads) in sixteen patients (51.6 per cent), including the patient with an isolated tricuspid lesion whose \hat{A}_P was situated at +75 degrees. In nine patients (29 per cent) the \hat{A}_P fell between 0 and +60 degrees (P positive in V_L and positive, isoelectric, or diphasic in V_F). In six patients (19.4 per cent) the \hat{A}_P fell between 0 and +60 degrees (P positive in V_L and negative in V_F). The average \hat{A}_P in all patients studied was +45 degrees. In six patients who were studied electrocardiographically on several occasions, a right deviation of \hat{A}_P was observed in the course of disease and reached 20, 30, 45, 50, and 100 degrees, respectively.

In the precordial leads, P was diphasic in V_1 , V_2 , and, in a few cases, in V_3 in all but one patient. Tracings made in the patient with isolated tricuspid disease are shown in Fig. 2.

The mean manifest axis of QRS (\hat{A}_{QRS}) deviated toward the right (between +90 and +150 degrees) in forty-one patients (93.2 per cent). The average \hat{A}_{QRS} was +103 degrees; in the patient with isolated tricuspid valvulitis \hat{A}_{QRS} fell at +105 degrees. In three patients \hat{A}_{QRS} fell between 0 and +90 degrees; the average \hat{A}_{QRS} was +99 degrees.

The mean manifest axis of T (\hat{A}_T) was determined in twenty-two patients whose electrocardiograms showed no alteration of the S-T segment and no influence of digitalis upon the T wave. In eleven patients (50 per cent) \hat{A}_T was between 0 and -90 degrees; in the patient with pure tricuspid disease \hat{A}_T was 0 degree. The average \hat{A}_T of the group was -28 degrees. In the remaining eleven patients (50 per cent) \hat{A}_T fell between 0 and +90 degrees, with an average of +40 degrees. The average \hat{A}_T for all twenty-two patients was +12 degrees.

The time of onset of the intrinsic deflection in V_1 and V_2 was 0.04 second or more in twenty-eight patients (63.63 per cent); in the remaining sixteen patients the time was less than 0.04 second. In the patient with the isolated lesion the time was 0.07 second in V_2 and 0.06 second in V_1 (Fig. 2). The average time registered in V_1 and V_2 in all patients was 0.041 second, the maximum being 0.07 second and the minimum, 0.01 second.

Certain other findings are of interest. On several occasions we found a negative T wave in the right or left or in all precordial leads and a deep S wave in V_5 and V_6 . Because of the small number of cases, no attempt is made to analyze these findings.

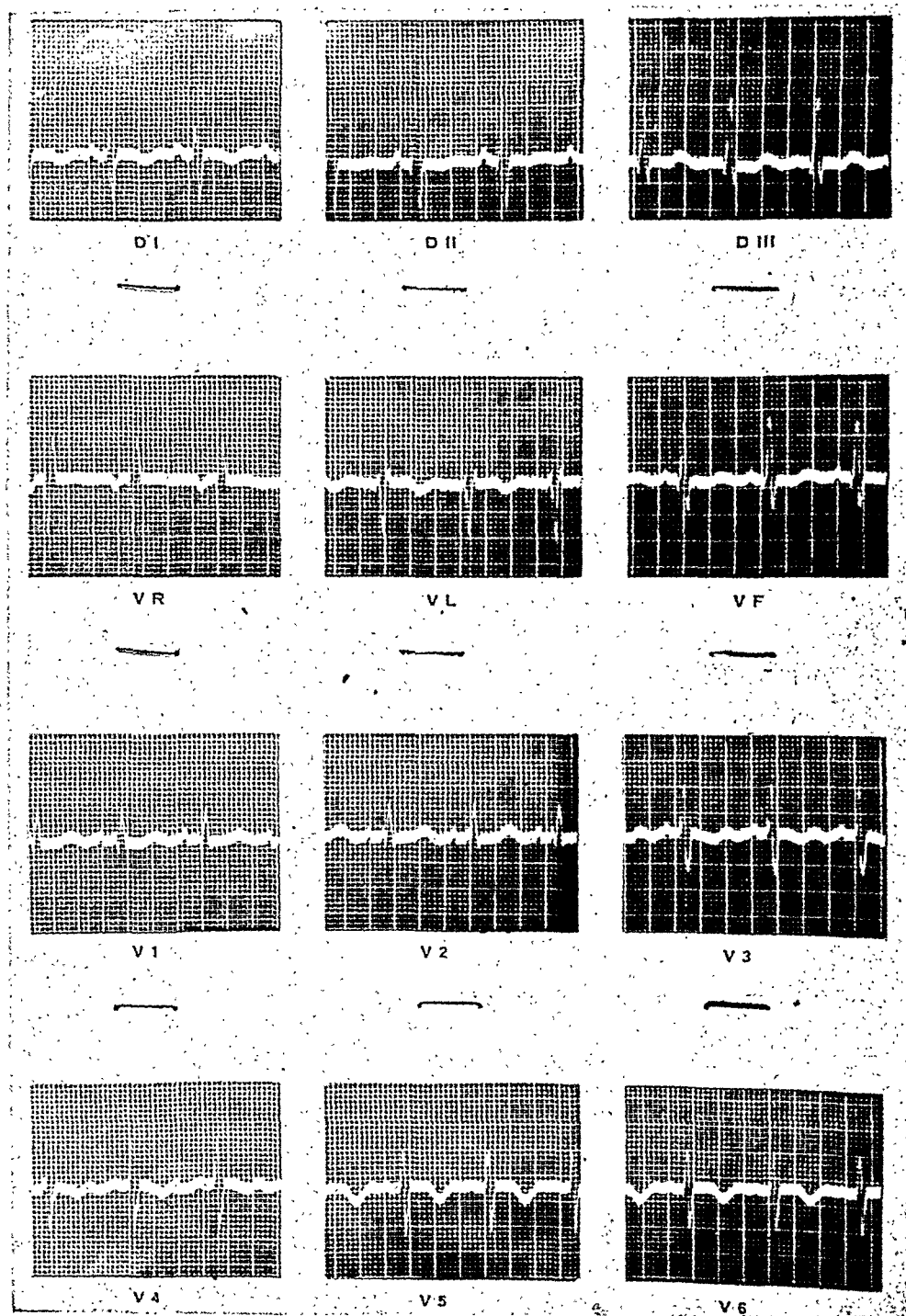


Fig. 2.—Tricuspid insufficiency without other valvular lesions.

*X-ray Signs.**—The x-ray findings must be divided in two different groups: dynamic and static signs. Since the majority of patients had aortic insufficiency, the dynamic signs characteristic of this condition were present. In two patients, however, who had mitral and tricuspid lesions without aortic involvement, dynamics of the aortic type were observed. In the patient

*We are indebted to Dr. N. Dorbecker, Chief of the X-Ray Department, for his valuable suggestions and criticisms.

with isolated tricuspid involvement whose blood pressure was 110/0, the aortic type of phenomena was observed; it is possible that some other lesion in the peripheral circulation (arterio-venous fistula?) capable of producing such phenomena was present.

The static findings were as follows: In twenty-two of the forty-five patients (48.88 per cent) the right atrium was clearly increased in volume (grades 2 to 4). In the patient with pure tricuspid disease the enlargement was considered to be grade 3. In twenty-five of the forty-five patients (55.55 per cent) the left atrium was enlarged (grades 2 to 4). In these twenty-five patients the tricuspid disease coexisted with mitral stenosis. The patient with pure tricuspid disease did not show left atrium enlargement. In twenty of the forty-five patients (44.44 per cent) the right ventricle was enlarged (grades 2 to 4). The patient with isolated tricuspid disease had grade 3 enlargement.

The pulmonary arch showed definite but not extreme prominence in seventeen patients (including the patient with tricuspid disease); a more prominent arch was present in seven patients. The hilar shadows were accentuated in thirty-three (73.33 per cent) patients. A double contour of the right cardiac silhouette was present in nine patients (17.17 per cent). There were five additional patients in whom a visible right bronchus simulated a double contour. The esophagus was not deviated to the left in any patient. The lungs were normal in seven patients (15.55 per cent), despite the fact that all had serious mitral disease. In eight patients the superior vena cava was dilated in anteroposterior and right oblique positions.

In patients in whom kymographic studies were made, no atrial contour indentations of ventricular type were observed, although the auricles showed increased pulsations.

COMMENT

Our experience with cardiac patients, particularly those with chronic rheumatic disease, has convinced us that the effort to determine with precision the number of valves affected and the degree and type of involvement is of more than academic importance. It is our conviction that if the condition of the myocardium is fundamental in the production of cardiac failure, then disease of the valves constitutes a prime factor in producing the failure of the myocardium and is the determining cause of the type of heart failure which develops in the course of chronic valvulitis. We feel, therefore, that the concepts of the English school are not altogether correct. MacKenzie and Lewis emphasized the lack of importance of valvular lesions. This is the exact antithesis of the teaching of Levine,¹² who maintains that valvular lesions are of highest importance in chronic rheumatic heart disease and are more important than the myocardium as a primary cause of cardiac insufficiency in patients with rheumatic heart disease, except when acute carditis is present. We believe that Levine's opinion justifies every effort to diagnose valvular lesions with precision.

Although our autopsy experience had shown that clinical study failed to recognize many tricuspid lesions, nevertheless, we were surprised that in a large series of patients with rheumatic heart disease, 33.3 per cent had sufficient involvement of the tricuspid valve to make diagnosis possible. This figure can be raised to 50 per cent if we include the patients with slight valvular endocarditis which did not deform the valve and which did not cause functional derangement. (In the latter group, diagnosis is impossible.)

This incidence (33.3 per cent) is higher than that published by some other authors.^{6,7,9,11} Combs (cited by Cooke and White¹³), however, gives a higher incidence: thirty-five of ninety-seven patients with rheumatic heart disease. Von Glahn in 1927 (cited by White and Cooke¹³) found forty-one examples of

tricuspid involvement in 109 rheumatic patients. Libman found an incidence of 60 per cent in eighteen patients. Thayer (1929) found an incidence of 44 per cent.

Herrmann has stated⁶ that the tricuspid valve is involved in 25 to 30 per cent of patients with chronic rheumatic valvular disease (we found 49 per cent) and that in two-thirds of such patients there is only slight valvular damage. Bland, Jones, and White¹⁴ found tricuspid lesions in thirty-one of 100 rheumatic patients. In thirty of 217 cases of rheumatic heart disease, White and Cooke¹³ found the valvular lesion sufficiently marked to give clinical signs. Garvin¹¹ found tricuspid involvement in 36.1 per cent of 119 rheumatic patients. In 10.9 per cent the involvement was sufficiently advanced to produce an actual stenosis.

It is obvious that the figures we present, based on autopsy findings, pertain, by definition, to seriously ill patients with advanced disease and, consequently, do not give a true picture of the clinical frequency of these lesions. However, the figures given by other authors were also obtained from autopsy findings. Our study finds justification in the fact that one of every three patients with advanced rheumatic heart disease has lesions in the tricuspid valve.

So rare is the isolated tricuspid lesion that we found it in only one case and it was not rheumatic. It was an extraordinary case for many reasons. In all other cases other valves were involved. In 44 per cent the tricuspid lesion was associated with mitral lesions (stenosis, insufficiency, double lesions), in 54 per cent with mitral and aortic lesions, but only in 2 per cent with lesions of the other three valves.

This coincidence with other better known lesions of clearer symptomatology explains in part why tricuspid damage is so often unrecognized. This association of tricuspid lesions with other valvular lesions is so frequent that Shattuck, quoted by Futcher,¹⁰ proposed that the diagnosis of tricuspid disease be made on the basis of this association: "Whether or not you hear a presystolic murmur of tricuspid stenosis it can surely be diagnosed, if the patient is a woman with rheumatic antecedents, *if she has mitral and possibly aortic stenosis* and gives evidence of prolonged and recurring venous stasis."

The clinical diagnosis of the tricuspid lesion was correctly made in 34 per cent of our series. Even though it is a low percentage, it is nevertheless higher than that found in other studies we have been able to consult and serves to emphasize how rarely the diagnosis is made.

There is nothing unusual in respect to the age of our patients. The age corresponds to that found by other authors and is about the same as that obtained by Cortés and Villarreal³⁵ in rheumatic patients with other types of heart lesions. The same can be said concerning the role of sex, since mitral disease also predominates in women. The average duration of life in the patients of our series differs decidedly from that given by Levine. This makes us doubt the compensating effect of the tricuspid lesion and its action in prolonging life.

Dyspnea was an almost constant finding, being absent in only 4 per cent of the patients. Nevertheless, its intensity was of a lesser degree than is commonly found in patients with rheumatic lesions who are as seriously ill as the patients of our series but who do not have tricuspid involvement. This suggests that the reduction of the output toward the pulmonary artery due to the tri-

cuspid lesion exempts the lungs, to some extent, from marked congestion, such as would be produced if the effects of the associated lesions were not neutralized in part by the tricuspid lesion, which acts as a sort of "safety valve."

The low incidence of paroxysmal dyspnea was remarkable. Dyspnea of decubitus was present in 60 per cent of the cases but absent in 40 per cent of seriously ill patients with mitral disease. This interesting finding was very often useful in diagnosis. Involvement of the tricuspid valve is suggested when a cyanotic patient with distended veins, at times with edema and ascites, is able to maintain recumbency without discomfort. This clinical feature, we discovered later, had been described by Duroziez in 1868.

Cough was not a constant finding. It was absent in 30 per cent of the patients. This is also an unusual finding in patients with severe cardiac insufficiency. Its absence has the same significance as the inconstancy of dyspnea.

Cyanosis, on the other hand, was found in varying degree in the majority of patients (56 per cent). It is fundamentally caused by the stasis and therefore belongs to the peripheral type of cyanosis.

The combination of pallor, cyanosis, and jaundice was present in only 8 per cent of our series. This combination gives the patient a very special appearance, as if he were under a mercury vapor lamp. This peculiar color was considered to be very characteristic by Shattuck. Wearn regarded it as a pathognomonic sign. Christian referred to it repeatedly.¹⁸⁻²⁰ We have observed this peculiar color, which might be called "Shattuck's sign," and have found it in association with tricuspid disease in some patients. However, the low percentage incidence in our series suggests that it is not a very common finding in tricuspid disease. Nor is it pathognomonic of tricuspid disease because it also may be found in other clinical conditions, such as constrictive pericarditis and sclerosis of the mediastinum.

Venous distention is one of the most important clinical signs because it is both frequent and outstanding. It was particularly constant in the neck veins where it was found, in greater or lesser degree, in 86 per cent of our patients. The presence of distended cervical or even facial veins in a patient lying in bed without evidence of dyspnea should suggest involvement of the tricuspid valve if one can eliminate certain other conditions, such as constrictive pericarditis, in which the venous return into the right auricle is impaired. Jugular distention often gives these patients a particular sensation of plethora and cervical pressure that is very uncomfortable.

The typical jugular pulsation was mentioned in the histories of only eighteen patients (36 per cent) of our series. In the remaining patients it is possible the sign was overlooked. It is also possible that the sign was absent. Absence of pulsation can occur⁵ but is difficult to explain. The decrease of the pulse in decubitus, also noted by other authors, we attribute to the permanent increase of pressure within the vessel, which, with a lesser degree of filling, permits wider variations of pressure in the different phases of the cardiac cycle and which, in turn, determines wider excursions of the vessel during systole. This amplitude of the jugular pulse, its occurrence in systole, and the frequent coincidence of

aortic insufficiency make it quite easy to confuse a venous pulse with the Corrigan type of pulse in the carotid arteries.¹⁸

In the phlebogram it has been shown that the jugular and other venous pulses²¹ are characteristic and give an exaggerated C wave without the sustained waves of stasis that join the C and V waves. White and Cooke¹⁸ have described a type of deep jugular pulse, seen in the phlebogram, which they believe to be a pathognomonic sign of tricuspid disease, when it is associated with chronic and constant congestion of the systemic veins. In the phlebogram a wide wave of stasis is observed in the rapidly ascending limb of the systolic evaluation. We did not find this wave.

The venous pulse in the forearm which Levine³ has called the most constant and suggestive clinical finding, and to which MacMillan has attached so much value, was not mentioned in the histories of any of our patients who were studied at necropsy. One of us looked for it carefully in thirty other patients who were not autopsied and found it present in only four patients.

Edema was almost as common as jugular distention. It was found in 84 per cent of our series. This is readily explained since these patients had typical congestive heart failure. In 48 per cent there was ascites, although in only 16 per cent was generalized edema present. This is also easily explained on the basis of portal hypertension. In 100 per cent of the patients hepatomegaly was present, and in 90.9 per cent the consistency of the organ was increased.

Hepatomegaly is of great importance in the diagnosis of tricuspid disease because it is so common and its pathogenesis so well understood. This carries such clinical weight that in a patient who has recovered from heart failure but has a persistently large liver we can suspect participation of the tricuspid valve among the valvular lesions. Hepatojugular *reflux* was not mentioned in any of the histories. Together with physical modifications of the liver, we found, in the cases so studied, a functional deficiency proved by the different tests, particularly the test of pigmentary function. This explains the special color of these patients. Crises of hepatic pain and frequent vomiting, not related to digitalis intoxication, were observed more often in combined mitral and tricuspid disease than in mitral disease alone. In addition to actual pain, a sensation of heaviness and fullness in the upper part of the abdomen was a common symptom in our series of patients.

A *seesaw movement* involving the apex and xiphoid area (Fig. 3) such as was described by Lang and by Dressler,²²⁻²³ was seen in only a few patients. In more patients we found a *systolic heave of the lower part of the sternum* produced by hypertrophy of the right cavities.

Undoubtedly the presence of a systolic murmur in the tricuspid region supercedes in importance all other signs and constitutes the strongest basis for the diagnosis of tricuspid disease. The proof of this lies in the fact that the seventeen patients (34 per cent) in whom the diagnosis was correctly made all had a systolic murmur. It is not always easy to detect this murmur because of the constant coincidence of a mitral murmur. In eight patients, however, both murmurs could be clearly recognized and differentiated by differences in intensity and timbre and by the location at which each murmur could be heard best. In the

other patients, the recognition of the murmur required the employment of the special technique which has been described.²⁵ This, we believe, has a great clinical value.

The intensity of a systolic murmur heard over the tricuspid region is increased during a deep, held inspiration only when the murmur originates in the tricuspid valve. The increase in intensity is explained by the increase of the negative intrathoracic pressure during inspiration which increases the blood flow toward the venae cavae and augments the blood velocity. This dynamic factor necessarily produces an increase of the pre-existing organic murmur.

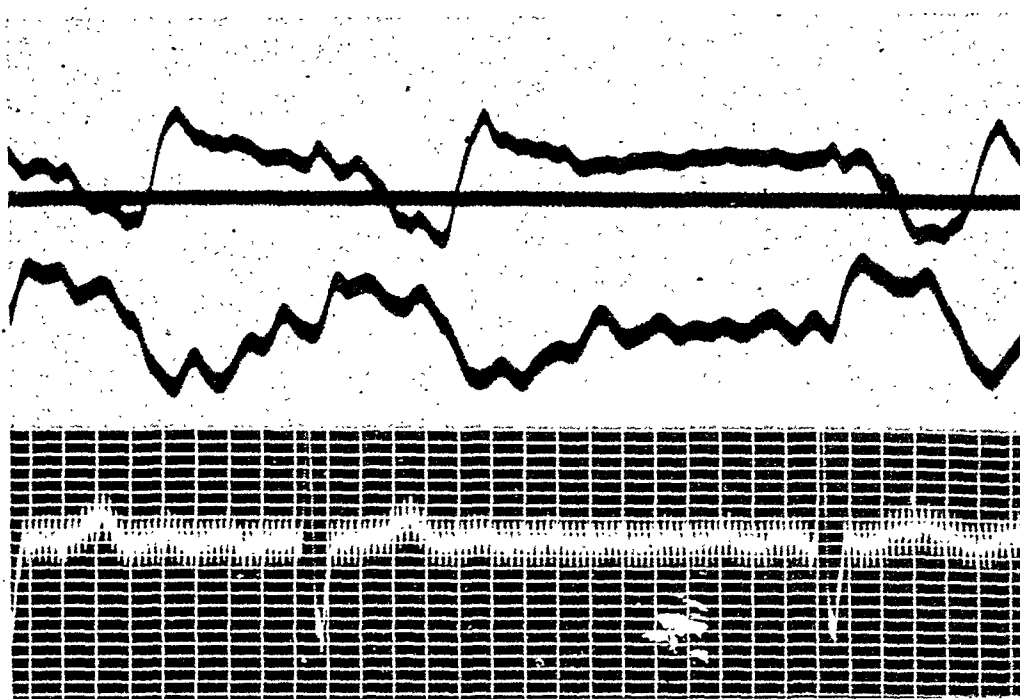


Fig. 3.—Upper tracing, apex cardiogram. Middle tracing, xiphoid cardiogram. Lower tracing, electrocardiogram, Lead II.

Interposition of the expanded lung between the heart and the point of auscultation does not affect tricuspid murmurs, since these murmurs are heard at a point where no pulmonary tissue exists. The descent of the diaphragm in inspiration tends to bring the portion of the heart in which the murmur originates nearer to the point at which the stethoscope is placed.

In contrast, a systolic mitral murmur is generally not intensified and may even be diminished during a deep, held inspiration. The increase of the output of the right side of the heart that follows inspiration does not affect the left side of the heart in the same abrupt and direct way in which increased venous filling affects the right heart because of the interposition of the lungs. Furthermore, inspiration, by increasing the volume of the pulmonary appendage located between the apex of the heart and the chest wall, can decrease the intensity of the acoustic phenomena which occur at the apical region.

In general, this method was useful, and when it gave clearly positive results, it was decisive in the diagnosis. Up to the present, in all autopsied patients in

whom the Rivero Carvallo sign had been positive, a tricuspid lesion was found. We believe an early diagnosis can be made in 80 per cent of patients with tricuspid involvement, even though late manifestations of increased venous pressure, which would facilitate diagnosis, may not have appeared.

The electrocardiographic signs found permit us to conclude that this method of study can, at times, help in the elaboration of the diagnosis or give a hint of the diagnosis which can be reached by other means. Here again one meets the difficulty created by the presence of concomitant mitral lesions which alone can alter the electrocardiogram in a similar but not in an identical way. The morphologic alterations and alteration of the voltage of the P waves can be found in pure mitral valvulitis, in the pure tricuspid valvulitis, and in the associated forms.

However, an average deviation of the axis of the P wave toward the right (above 60 degrees) in a patient with mitral disease who does not show clinical evidence of associated cor pulmonale strongly suggests the existence of a concomitant tricuspid lesion. Unfortunately, a large number of patients with tricuspid involvement have auricular fibrillation (29.5 per cent in our series) which prevents the use of this sign. Furthermore, it was positive in only 51.6 per cent of our patients. It is well known that mitral diseases, by creating left auricular hypertrophy, displace \hat{A}_P to the left with the result that the great majority of these patients have an average P axis deviation to the left of 58 degrees. However, there are exceptions to this rule and so the finding of \hat{A}_P to the right of this limit in mitral disease, even without added cor pulmonale, if not pathognomonic, is at least suggestive of a tricuspid lesion. Theoretically, the observation in serial tracings of progressive deviation, more or less rapidly, of \hat{A}_P toward the right in the course of active rheumatic disease, as we have observed several times, is of more diagnostic value.

A diphasic P wave is commonly observed in precordial leads of patients with left auricular hypertrophy which is frequently a result of mitral disease. Such diphasic P waves are also found in patients with tricuspid disease; we were able to verify this in one case of pure tricuspid disease. This sign, which has recently been described by Ellis and Brown,⁴⁰ we do not believe to be of value because of the common association of tricuspid and mitral valve disease.

The deviation of the \hat{A}_{QRS} to the right and of \hat{A}_T to the left, often found in our series, commonly occurs in patients with mitral disease alone and for this reason does not have diagnostic importance. On the other hand, a delayed onset of the intrinsic deflection in V_1 and V_2 of more than 0.04 second, which we found in 62.62 per cent of our patients (including the patient with pure tricuspid disease), seems to have more diagnostic importance. To evaluate this sign correctly it is necessary to determine the frequency of its occurrence in other conditions, such as pulmonary stenosis, arteriosclerosis, or pulmonary arteritis. Pellon, who was the first to call attention to the intrinsic deflection in the right precordial leads and who is now investigating this subject, has the impression that whenever there is a delay in the onset of the intrinsic deflection in V_1 and V_2 in a patient with rheumatic heart disease, there exists a tricuspid lesion, if right bundle branch block is not present.

The dynamic signs revealed by radiologic study of several of our patients with mitral and aortic disease can confuse the diagnosis. In patients with aortic, mitral, and tricuspid lesions, dynamic pulsations of the aortic type have an obvious explanation, but such dynamic pulsations found in those without aortic lesions may have different causes: (1) A dynamic pulsation of the apex may result when the left border of the cardiac contour is formed by a greatly hypertrophied right ventricle, the movements of which are influenced by tricuspid regurgitation. (2) Tricuspid insufficiency may cause dilatation and systolic pulsation of the superior vena cava. In the right anterior oblique position, the superposition of the shadows of the cava and the aorta give the impression of a single arterial vessel which is widened and hyperpulsatile. Careful x-ray study of the superior vena cava from various angles will lead to the correct diagnosis.

The x-ray study of the diaphragm in several patients with clinical diagnosis of tricuspid lesion has brought to our attention a useful sign: the diaphragmatic pulse, which is really the hepatic pulsation transmitted to the diaphragm.

Hypertrophy of the right auricle was frequent. Quite often hypertrophy of the left auricle was also present. When the double contour of the right auricular shadow was real, we could explain it by the *incomplete superposition* of the auricles whose enlargement was unequal. This idea is confirmed by the observation of the angiocardiographic films made by Dorbecker, employing the special technique of Celis.³⁹ This x-ray image, not constant, we believed to be of diagnostic value in tricuspid disease, but in this series of autopsied cases, it was not used.

One of the simplest and most valuable x-ray findings was the globular configuration of the cardiac silhouette in the anteroposterior position. Frequently, the shadow is triangular and suggestive of pericarditis with effusion except that there is no widening of the shadow of the base of the heart.

The pulmonary fields were clear in 15.55 per cent of our patients, many of whom had mitral disease with severe heart failure. This explains the relative insignificance of the dyspnea, the low frequency of decubitus dyspnea, and the absence of paroxysmal dyspnea in these patients with advanced cardiac insufficiency.

SUMMARY AND CONCLUSIONS

An analysis has been made of the signs and symptoms in fifty patients with severe tricuspid lesions confirmed by autopsy. These fifty patients comprised 33.33 per cent of all rheumatic cases that were found in 250 autopsy reports at the National Institute of Cardiology (Mexico).

A correct clinical diagnosis was made in 34 per cent of the tricuspid cases.

The most important facts found in this study were the following:

1. In all cases with rheumatic etiology, the tricuspid lesion co-existed with a mitral lesion; in many cases an aortic lesion was also present. Only exceptionally were all four valves involved.
2. A systolic murmur, heard over the xiphoid, constituted the basis of the diagnosis of tricuspid disease in all patients in whom the lesion was recognized in life.

3. In eight patients the fact that a tricuspid as well as a mitral murmur was present was determined by the fact that the acoustic characteristics were distinct in the mitral and tricuspid areas. This was appreciated without employing special technique.

4. In ten patients the modifications of the xiphoid systolic murmur produced by deep inspiration and by postinspiratory and postexpiratory apnea (method of Rivero Carvallo²⁵) were studied. In 90 per cent of the patients thus studied, the murmur increased in intensity during postinspiratory apnea; in several cases also the murmur became higher pitched during the held inspiration. A deep, held inspiration generally had the opposite effect upon a mitral systolic murmur. This fact was of great help in recognizing the tricuspid origin of the murmur.

5. A number of clinical manifestations which together or singly aid in the recognition of tricuspid involvement are discussed.

6. The only constant finding in our series was hepatomegaly of varying degree and character. In 90 per cent of the patients the consistency of the enlarged liver was increased.

7. The other signs, although at times more specific, are found less often. The striking infrequency of dyspnea of decubitus and of paroxysmal dyspnea, despite the presence of severe cardiac insufficiency, is undoubtedly related to the fact that the lung fields did not show x-ray evidence of congestion in 15.55 per cent and that no cough was present in 30 per cent of the patients with tricuspid disease. The color resulting from the combination of cyanosis, pallor, and sub-clinical jaundice, as described by Shattuck, was observed in only 8 per cent of our patients. We observed cyanosis alone in 56 per cent, distention of the jugular vein in 86 per cent, systolic jugular pulse in 36 per cent, and hepatic pulsation in 42 per cent. Among those patients subjected to liver function tests, 75 per cent showed functional deficiency.

8. Two electrocardiographic signs were found to be suggestive of a tricuspid lesion: the first consists in a deviation of \hat{A}_r to the right of more than 60 degrees (51.6 per cent) and the second, in a delay of 0.04 second or more in the onset of the intrinsic deflection in V_1 and V_2 (63.62 per cent).

9. The most important x-ray signs in the order of their clinical value and frequency were marked hypertrophy of the right auricle (48.88 per cent) or right ventricle (44.44 per cent); dynamic pulsations of the aortic type in the absence of an aortic lesion (4 per cent); double contour in the region of the right auricular salient, not produced by interposition of the right bronchus (17.77 per cent); dilatation of superior vena cava (17.77 per cent); triangular or globular appearance of the cardiac silhouette in the anteroposterior view.

10. It is concluded that the diagnosis of a tricuspid lesion, so infrequently made in the patient, can be made successfully by ordinary clinical methods in the majority of the cases.

REFERENCES

1. Winsor, T., and Burch, G. E.: Study of Incidence of Tricuspid Regurgitation at Large General Hospital in the South, South. M. J. 35:1065, 1942.
2. Kerr, W. J., and Morrison, L. F.: Tricuspid Disease, California & West Med. 26:193, 1927.
3. Levine, S. A.: Clinical Heart Disease, Philadelphia, 1937, W. B. Saunders Co., pp. 78-80.
4. Lewis, Sir Thomas: Disease of the Heart, New York, 1937, The Macmillan Co., p. 144.
5. Clements, A. B.: Isolated Tricuspid Stenosis of Probable Rheumatic Origin. Report of A Case With Unusual Clinical and Pathological Findings, Am. J. M. Sc. 190:389, 1935.
6. Herrmann, George: Oxford Medicine, London, 1921, Oxford University Press, vol. 2, chap. XII-A, p. 492.
7. Luisada, A. A.: Cardiología, Edit. Alfa, Buenos Aires 1945, p. 303.
8. Smith, J. A., and Levine, S. A.: The Clinical Features of Tricuspid Stenosis, AM. HEART J. 23:739, 1942.
9. Mackenzie, Sir James: Oxford Medicine, London, 1921, Oxford University Press, vol. 2, p. 464.
10. Fitcher, T. B.: Tricuspid Stenosis With Report of Five Cases, Am. J. M. Sc. 142:625, 1911.
11. Garvin, C. F.: Tricuspid Stenosis: Incidence and Diagnosis, Arch. Int. Med. 72:104, 1943.
12. Levine, S. A.: The Great Importance of Valvular Injury in Rheumatic Heart Disease, in Libro Homenaje al Prof. I. Chávez, Mexico, D. F., 1945, Edición de el Colegio Nacional, p. 185.
13. Cooke, W. T., and White, P. D.: Tricuspid Stenosis With Particular Reference to Diagnosis and Prognosis, Brit. Heart J. 3:147, 1941.
14. Bland, E. F., Jones, T. D., and White, P. D.: The Development of Mitral Stenosis in Young People, AM. HEART J. 10:995, 1935.
15. Cabot, R. C.: Facts on the Heart, Philadelphia, 1926, W. B. Saunders Co.
16. Vander Veer, J.: Stroud's Diagnosis and Treatment of Cardiovascular Disease, Chronic Valvular Disease, Tricuspid Valvular Disease, Philadelphia, 1945, F. A. Davis Co., p. 380.
17. Herrick, W. W.: Tricuspid Stenosis With Report of a Cure, Arch. Int. Med. 2: 291, 1908.
18. White, P. D., and Cooke, W. T.: The Recognition and Significance of Marked and Chronic Systolic Pulsation of the Deep Jugular Veins, Tr. A. Am. Physicians 54:199, 1939.
19. Christian, H. A.: The Diagnosis and Treatment of Diseases of the Heart, in Oxford Medicine, New York, 1940, Oxford University Press, p. 163.
20. Osler, William: The Principles and Practice of Medicine, by Henry A. Christian, ed. 15, Philadelphia, 1944, D. Appleton Co., p. 1058.
21. White, P. D.: Heart Disease. Tricuspid Valve Disease, New York, 1944, The Macmillan Co., p. 629.
22. Dressler, Wilhelm: Pulsations of the Wall of the Chest. I. General Consideration, Arch. Int. Med. 60:225, 1937.
23. Dressler, Wilhelm: Pulsations of the Wall of the Chest. III. Pulsations Associated With Tricuspid Regurgitation, Arch. Int. Med. 60:441, 1947.
24. Chávez, I., and Rivero Carvallo, J. M.: Una nueva maniobra para diferenciar los soplos aórticos y los pulmonares, Arch. latino am. de cardiol. y hemat. 5:115, 1935.
25. Rivero Carvallo, J. M.: Comunicación a la Sociedad Mexicana de Cardiología, August, 1946.
26. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart. Tricuspid Valve Disease, Philadelphia, 1943, Lea & Febiger, p. 192.
27. Zeisler, E. B.: Tricuspid Stenosis. A Review of a Case With Antemortem Diagnosis, AM. HEART J. 8:697, 1933.
28. Yater, W. M., and Shapiro, M. J.: Congenital Displacement of the Tricuspid Valve (Ebstein Disease): Review and Report of a Case With Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System, Ann. Int. Med. 9:1043, 1937.
29. Altschule, M. D., and Blumgart, H. L.: The Circulation Dynamics in Tricuspid Stenosis, AM. HEART J. 13:589, 1937.
30. Friedland, R. D., and Kerr, W. J.: The Clinical Diagnosis of Tricuspid Stenosis, AM. HEART J. 15:625, 1938.

31. Cottin, E., and Saloz, C.: Tricuspid Stenosis, Arch. d. mal. du coeur 13:481, 1920.
32. Novelo, S.: Estudio comparativo de la onda P. en los enfermos mitrales y pulmonares crónicos, Arch. Inst. cardiol. México 15: 179, 1945.
33. Oigaard, A.: Tricuspid Stenosis, Arch. d. mal. du coeur 16:859, 1923.
34. Friedlander, R. D., and Kerr, W. S.: The Clinical Diagnosis of Tricuspid Stenosis, AM. HEART J. 11:357, 1936.
35. Cortés, C., and Villarreal, H.: A Study of Rheumatic Valvular Endocarditis, presented before the Interamerican Congress of Cardiology, Mexico City, October, 1946.
36. Taussig, B. L.: A Case of Tricuspid Stenosis With Enormous Dilatation of the Right Auricle, AM. HEART J. 14:744, 1937.
37. Ernstene, A. C., and Blumgart, H. L.: Orthopnea: Its Relation to the Increased Venous Pressure of Myocardial Failure, Arch. Int. Med. 45: 593, 1930.
38. Turnbull, H. H., and Weil, H. T.: The Auricular Form of Liver Pulsation and Its Relation to Tricuspid Stenosis, Heart, 3:243, 1911.
39. Chávez, I., Dorbecker, N., and Celis, A.: Direct Intracardiac Angiocardiology. Its Diagnostic Value; presented before the Interamerican Congress of Cardiology, Mexico City, October, 1946.
40. Ellis, G. M., and Brown, W. N.: Parasternal Leads in Tricuspid Insufficiency, AM. HEART J. 32:364, 1946.

Clinical Reports

CONGENITAL PULMONARY STENOSIS WITH CLOSED INTERVENTRICULAR SEPTUM

REPORT OF A CASE ASSOCIATED WITH PATENT FORAMEN OVALE AND SLIGHT TRICUSPID STENOSIS

STEWART H. AUERBACH, M.D., NASHVILLE, TENN., AND HARRY T.
HARPER, JR., M.D., AUGUSTA, GA.

IN MAUDE ABBOTT'S classic *Atlas of Congenital Cardiac Disease*¹ there are described nine cases of pulmonary stenosis in which all septa were closed and sixteen cases of pulmonary stenosis in which only the foramen ovale was patent. These two groups constitute the rarer forms of pulmonary stenosis as compared to the more numerous group in which the interventricular septum is defective. In 1942, Rossman² described an additional case of pulmonary stenosis with closed interventricular septum and patent foramen ovale in a 4-month-old child. He listed this as the eighteenth of its type, including Abbott's original sixteen. It is not clear whether this report includes a case reported by Blackford and Parker³ in which the foramen ovale was anatomically open, although considered to be functionally closed. To these may be added the case of Garrison and Feldt⁴ (all septa closed) and two cases (Cases 5 and 9) from a recent series by Currens, Kinney, and White,⁵ one with all septa closed and one with patency of the foramen ovale.

To that group of congenital pulmonary stenosis with closed interventricular septum but patent foramen ovale we wish to add the case which will be described.

CASE REPORT

H. K., a 15-year-old white boy, was first admitted to the University Hospital on Sept. 10, 1940. He complained of painful swelling of the glands of the left axilla, and of fever, headache, and general malaise of about two weeks' duration. Physical examination relative to these complaints revealed pharyngitis and generalized lymphadenopathy, one node in the left axilla being especially enlarged. The leucocyte count was 11,000 but nothing unusual was noted in the blood smear. Blood agglutination tests were negative, but a heterophil antibody reaction was not performed.

From the Departments of Pathology and Medicine, School of Medicine, University of Georgia, Augusta, Ga.

Received for publication April 30, 1946.

Examination directed attention to the cardiovascular system, and questioning brought out these points of importance. He had been "sickly" all of his life and had always suffered from shortness of breath. Climbing a single flight of stairs induced dyspnea. He had never been able to participate in the usual exercises or games of his companions. For several years he had had unexplained nose bleeds. There was no history of his having been a "blue baby," nor of cyanosis since birth. No history of rheumatic involvement was obtained. On examination he was somewhat malnourished. There was no cyanosis or clubbing of the fingers. The thorax was of the "pigeon-breast" type with an increased anteroposterior diameter. The lungs were clear. The blood pressure was 100/65. The heart was considered to be slightly enlarged, the left border of dullness being one centimeter beyond the midclavicular line. There was a loud systolic murmur over the entire precordium, with its point of maximum intensity over the second intercostal space to the left of the sternum. This murmur was well transmitted up the neck vessels on the left side and toward the left axilla. It was described as being "swishing or rasping" in quality. No mention was made of the intensity of the pulmonic second sound. Examination was otherwise essentially negative. An x-ray film of the chest (Fig. 1) showed fullness in the region of the



Fig. 1.—Teleroentgenogram showing the prominent pulmonary conus, hypertrophied right auricle, and the blunt apex indicative of right ventricular hypertrophy. Note the shadow of the great veins to the right of the sternum.

pulmonary artery and right auricle. The electrocardiogram (Fig. 2) showed intraventricular block with right axis deviation. The diagnosis made by the house staff at this time was possible patency of the ductus arteriosus and interventricular septum. The patient was discharged Oct. 13, 1940.

He was readmitted eighteen months later. In the interim he had experienced occasional attacks of dyspnea but had felt well until two weeks before admission when he developed frequency of urination, with reddish discoloration of the urine. At the same time his feet began to swell. Soon after, he noted swelling of the face and hands and he complained of persistent headache. Examination revealed moderate generalized edema. The blood pressure was 150/100. The heart findings were the same as those observed on the first hospital admission except that a systolic thrill, in addition to the murmur previously described, was noted. There was no ascites. There was Grade 3 edema of the ankles. Urine examination showed cellular elements and albumin, consistent with a diagnosis of acute glomerular nephritis. On this admission, a diagnosis of pulmonic stenosis with interventricular septal defect was made on the basis of the cardiac findings. The patient responded promptly to the routine treatment for nephritis and was discharged on April 26, 1941.

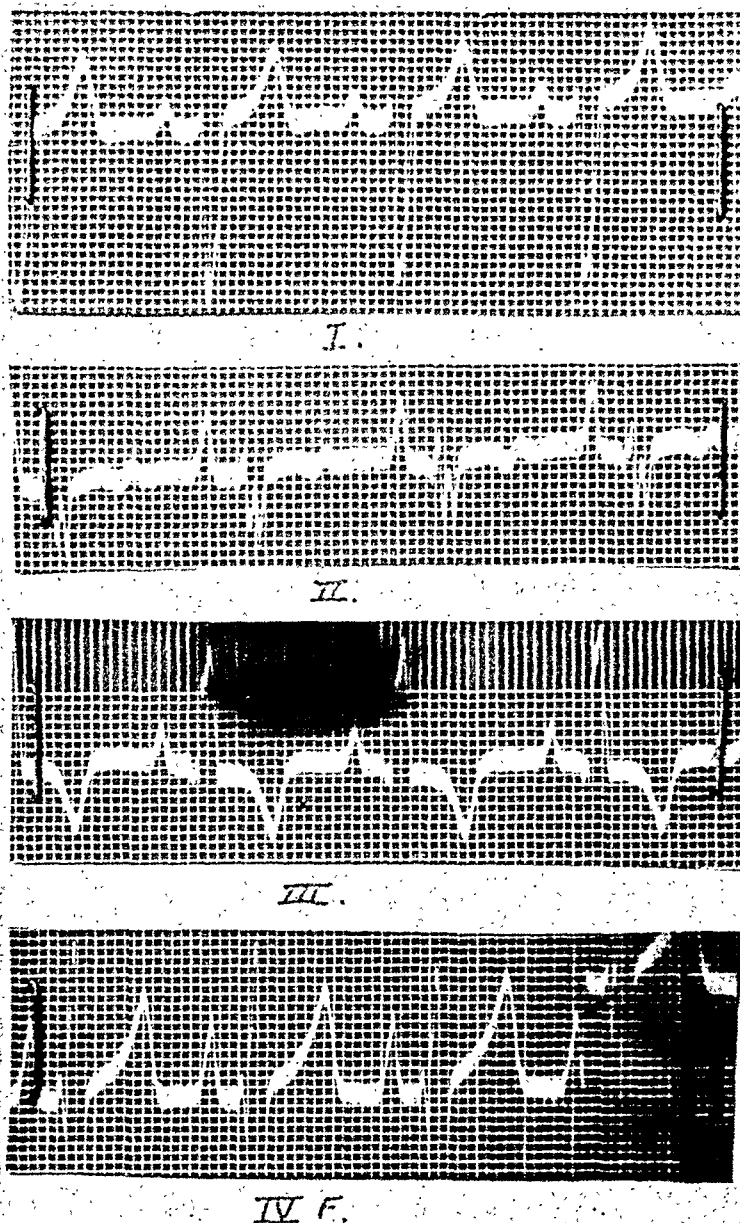


Fig. 2.—Electrocardiogram showing right ventricular preponderance, abnormally high P waves, and intraventricular block.

He was next admitted on Feb. 28, 1942, complaining of hemoptysis. Three weeks prior to admission he had developed a cold and cough and had begun to bring up small amounts of bright red blood. No cyanosis was noted. Pharyngitis and rhinitis were present. The heart was thought to be slightly enlarged. Auscultatory findings were as before. There was a mild degree of polycythemia, the red cell count being 6.2 million and the hemoglobin about 17 grams. For the first time a diagnosis of interauricular septal defect was made.

About one year later he was admitted again for acute pharyngitis. By this time cyanosis and clubbing of the fingers had appeared; the cyanosis was of moderate degree and the clubbing was minimal. Two distinct murmurs were now audible. One was maximal over the pulmonic area and was well transmitted along the left clavicle. The other was best heard over the third and fourth intercostal spaces to the left of the sternum. X-ray examination showed dilatation of the pulmonary artery, what was thought to be widening of the aorta to the right of the sternum, and enlargement of the right auricle. The electrocardiogram still showed intraventricular block and right axis deviation. The circulation time from arm to tongue was 14.5 seconds. Blood cultures and a blood Wassermann test were negative. A teleroentgenogram showed the following measurements: Midline to left border, 9.5 cm.; midline to right border, 4 cm.; total cardiac diameter, 13.5 cm.; and internal intrathoracic diameter, 24 centimeters. Mild polycythemia was still present. The diagnosis at this time was tetralogy of Fallot.

The next admission was on Jan. 19, 1944, for another attack of acute pharyngitis. Hemolytic streptococci were cultured from the nasopharynx. On this admission a diagnosis of tetralogy of Eisenmenger was made and this was maintained until the death of the patient. It was thought that all four cardinal points were clinically proved. The dilated pulmonary artery was visualized repeatedly both in films and under the screen. The interventricular septal defect was thought to be confirmed by the presence of intraventricular block in the electrocardiogram. Right ventricular hypertrophy was demonstrated by right axis deviation in the electrocardiogram and by the typical appearance of the x-ray shadow. Dextroposition of the aorta was thought to be seen in x-ray films and on the fluoroscopic screen. Cyanosis, clubbing, and polycythemia confirmed the impression of a venous-arterial shunt. Many clinics were held on this patient as a typical case of the Eisenmenger complex.

Three brief admissions late in 1944 are pertinent only in that it was evident that his cardiac reserve was becoming progressively less. Cyanosis was more marked. He was still able to work as a taxi driver. The final admission was on Nov. 11, 1945, when the diagnosis was acute upper respiratory infection and possible atypical pneumonia. He showed no evidence of heart failure on admission. The leucocyte count was 9,750 and the hemoglobin was 21 grams. On the following day there were moist râles throughout both lungs and a gallop rhythm was audible. Supportive treatment was without effect. Cyanosis increased and he died on Nov. 12, 1945, at the age of 20 years.

Necropsy.—The examination was performed about four hours after death. The unopened pericardial sac was much enlarged especially to the right and toward the base so that the outline was more globular than usual. There was a slight excess of clear serous fluid enclosed.

The heart weighed 520 grams. The transverse diameter across the ventricles was 13 centimeters. Inspection and palpation of the organ, in situ, disclosed pronounced preponderance of the right chambers, particularly of the ventricle. The right auricle was dilated and hypertrophied, far exceeding the left in volume and in thickness of muscle. The foramen ovale (Fig. 3) was freely patent from right to left in a slightly oblique direction, the defect measuring 1 x 0.6 centimeters. The tricuspid ring measured 10 centimeters. The valve was grossly deformed so that only two cusps (anterior and medial) were clearly identifiable. These were thickened and contracted and the chordae tendineae were correspondingly thickened and shortened; the anterior leaflet was somewhat more affected. On the line of closure were a number of small, discrete, firmly attached, moist fibrous nodules, the largest measuring about 0.3 cm. in its greatest diameter (Fig. 3). The right ventricle was of increased capacity. The muscle was greatly thickened, varying from 1.2 to 1.8 cm. in diameter. The bundles were coarsely hypertrophied and there were numerous minute fibrous scars. The conus appeared slightly narrowed but the lumen was not constricted.

The pulmonary valve was exposed from above and presented a remarkable picture of stenosis (Fig. 4). It was composed of three distinct cusps of equal size, but all were thickened and



Fig. 3.—View of the right chambers showing myocardial hypertrophy and tricuspid valvular disease. The arrow indicates the foramen ovale.

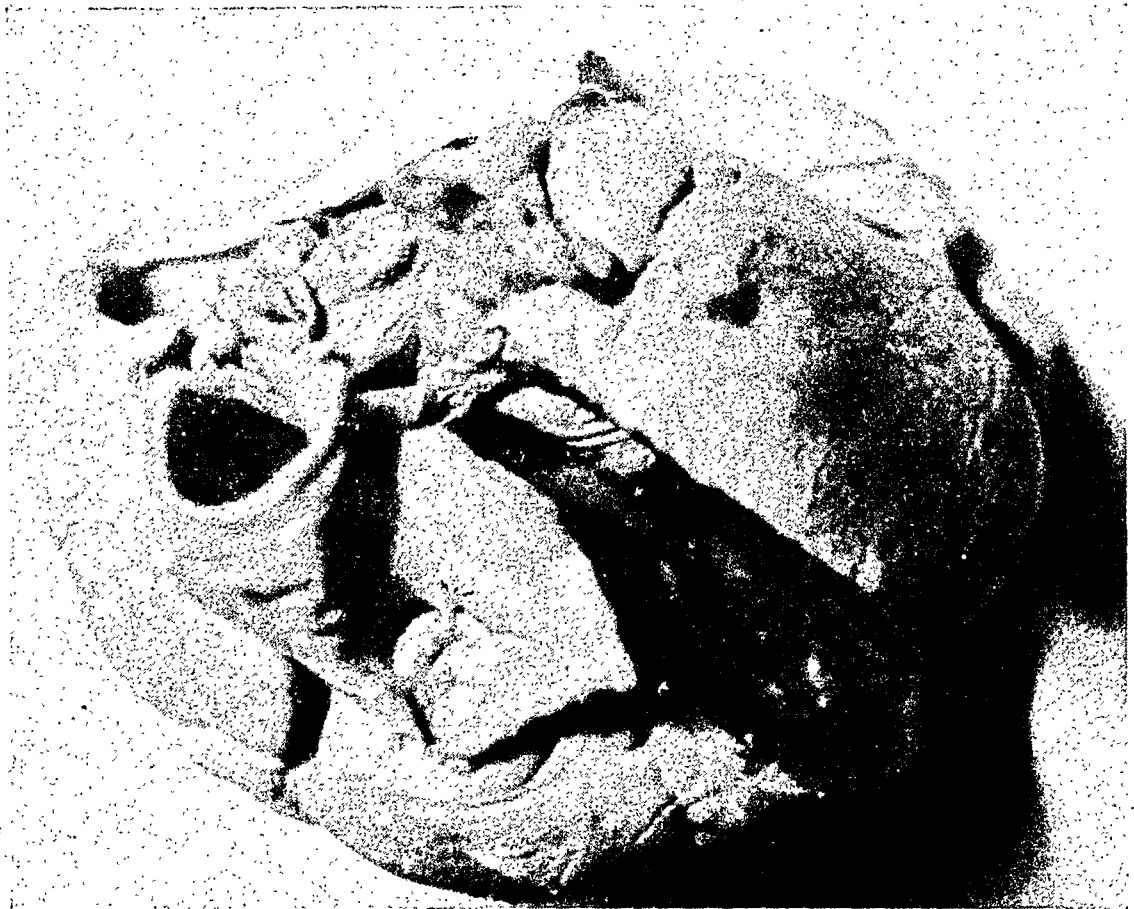


Fig. 4.—The pulmonary valve as seen from above with the artery opened and retracted. The degree of stenosis, although actually extreme, is slightly exaggerated in the fixed specimen.

fused together along the free edges so as to constitute a nearly complete diaphragm. In the center of this fused valve was a smooth rounded aperture, about 0.2 cm. in diameter when under slight tension. Water contained in the conus seeped through the valve very slowly. The ring measured 5.8 centimeters. The pulmonary artery was of about the same circumference and was essentially normal in structure and distribution of branches. The ductus arteriosus was closed.

The left chambers and valves were contrastingly normal on gross examination. There was slight dilation of the left auricle. The ventricular myocardium measured 1.2 cm. in thickness. The interventricular septum was intact. The mitral valve was well formed, of delicate structure, and fully competent. The aortic ring measured 6 centimeters. The valve cusps were thin and pliable. The sinuses and the coronary arteries were normal. There was very slight atheromatosis of the systemic aorta.

Microscopic study of the myocardium confirmed the hypertrophy and scarring of the right ventricular muscle. The fibrous scars were of very small size and of indiscriminate distribution. They appeared to be secondary to degeneration and atrophy of scattered muscle fibers since these changes were existent. There was some condensation and clustering of sarcolemma cells in such foci, and occasionally there were a few infiltrating round cells. There was no suggestion of rheumatic disease. The intimate vasculature was congested and there were scattered foci of recent interstitial hemorrhage. Slight interstitial edema was present. There was considerable loose fibrous thickening of the mural endocardium in one section.

A section of the tricuspid valve showed irregular fibrosis having a myxomatous character in some areas. An included marginal nodule was made up of similar myxomatous fibrous tissue. There were occasional round cells beneath the covering endocardium and around the dilated capillaries present in the valve leaflet proper.

The immediate cause of death was confluent lobular pneumonia. The left lower lobe was more affected and showed some areas of frank suppuration. Cultures were not obtained but masses of cocci were present in microscopic sections of the pulmonary lesions and in the overlying pleural exudate. The remainder of the examination revealed no important findings. There was evidence of chronic passive congestion of the abdominal viscera. The kidneys showed small healed infarcts. There was no evidence of pulmonary tuberculosis which has been described as being a frequent complication of pulmonary stenosis.⁶

COMMENT

In retrospect, the clinical diagnostic error was brought about by logical but false deductions on evidence pointing especially to two components of the Eisenmenger complex. Perhaps the most misleading feature was the assumption of interventricular septal defect on the basis of electrocardiographic evidence of intraventricular block. Blackford and Parker³ observed the same phenomenon in a strikingly similar case and were led into the same clinical error. We agree with them that the block was really produced by myocardial (conduction system) damage and that the probable cause was ischemia. A second confusing feature was the radiographic evidence of pulmonary artery dilatation; it now appears that this dilatation well might have been the so-called "dynamic dilatation," actually existent during life but, of course, not evident after death. It also appears that the radiographic fallacy of the dextroposed aorta was probably a shadow of the great veins. The correct clinical diagnosis might have been reached by the use of right heart catheterization to demonstrate abnormally high oxygen content of the auricular blood, or the employment of a contrast medium to accurately locate the septal defect. From the practical therapeutic standpoint, however, the diagnostic error was unimportant and for this reason these procedures may not have been entirely justifiable.

SUMMARY

An additional case of congenital pulmonary stenosis without ventricular septal defect is described. Functional patency of the foramen ovale and tricuspid valvular disease with minor stenosis were associated anomalies. The patient lived to be 20 years of age and developed overt circulatory deficiency only during the last two and one-half years of his life. Clinical diagnostic difficulty resulted from evidence of intraventricular block simulating septal defect.

REFERENCES

1. Abbott, Maude E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.
2. Rossman, J. I.: Congenital Atresia and Stenosis of Great Cardiac Vessels, *Am. J. Dis. Child.* 64:872, 1942.
3. Blackford, L. M., and Parker, F. P.: Pulmonary Stenosis With Bundle Branch Block, *Arch. Int. Med.* 67:1107, 1941.
4. Garrison, R. E., and Feldt, R. H.: Congenital Pulmonary Stenosis With Closed Cardiac Septa, *AM. HEART J.* 24:685, 1942.
5. Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary Stenosis With Intact Interventricular Septum, *AM. HEART J.* 30:491, 1945.
6. Auerbach, O., and Stemmerman, M. G.: The Development of Pulmonary Tuberculosis in Congenital Heart Disease, *Am. J. M. Sc.* 207:219, 1944.

FAMILIAL CONGENITAL COMPLETE A-V HEART BLOCK

MARTIN H. WENDKOS, M.D., AND ROBERT S. STUDY, M.D.
PHILADELPHIA, PA.

ALTHOUGH, over the past few decades many cases of congenital complete A-V heart block have been reported in the literature, Aylward was the first to suggest that there may be a familial predisposition to the development of such a conduction defect.¹ The basis for his opinion was his observation that a slow pulse rate (below 50 per minute) was present in each of two siblings shortly after their birth. At the time, however, corroborative electrocardiograms were not included. Subsequently, Aitken² stated that she had obtained electrocardiograms of both of Aylward's patients and had confirmed the existence of complete heart block. Unfortunately, reproductions of the records were not published. It is the purpose of this report, therefore, to demonstrate with the support of graphic evidence the occurrence of complete congenital A-V heart block in two siblings, one parent of whom suffered from the effects of a different type of anomalous conduction (Wolff-Parkinson-White syndrome).

CASE REPORT

The 33-year-old father of the two children, whose case histories are to be reported in detail, first came to the attention of one of us (M. H. W.) early in 1943. At that time he was troubled with attacks of paroxysmal tachycardia from which he had been suffering for the past fifteen years. An electrocardiogram was obtained during one of his attacks, and the diagnosis of a supraventricular form of paroxysmal tachycardia was confirmed (Fig. 1). Records made after subsidence of the attack showed that he was suffering also from an anomaly of conduction characterized by a short P-R interval and a bizarre QRS complex (Fig. 1). Electrocardiograms of his wife and his dizygotic twin brother were entirely normal (Fig. 2).

Several weeks later his first child, then five years of age, was brought to one of us (M. H. W.) for an examination because of the fact that he had been known to have a slow heart rate (less than 60 per minute) since the age of two. This bradycardia was first discovered by the attending physician when the child was being treated for a simple respiratory infection. As far as the parent was aware, the child had suffered no ill effects as the result of this slow heart rate and had always been able to play and exercise without disability or cyanosis. He had had none of the usual cardiotoxic diseases, such as diphtheria, scarlet fever, or rheumatic fever. His mother had not been ill during his fetal life, and birth was spontaneous and uncomplicated. The electrocardiogram, which was made when he was five years of age, showed the presence of complete A-V heart block, with a ventricular rate of 60 per minute (Fig. 3). The physical examination revealed no significant changes other than the bradycardia, which was not materially modified by exercise. X-ray studies of the heart and lungs demonstrated no abnormalities. A brother,

From the Division of Cardiology, Philadelphia General Hospital, Medical Division, Pennsylvania Hospital, and the School of Medicine, University of Pennsylvania.

Received for publication July 9, 1946.

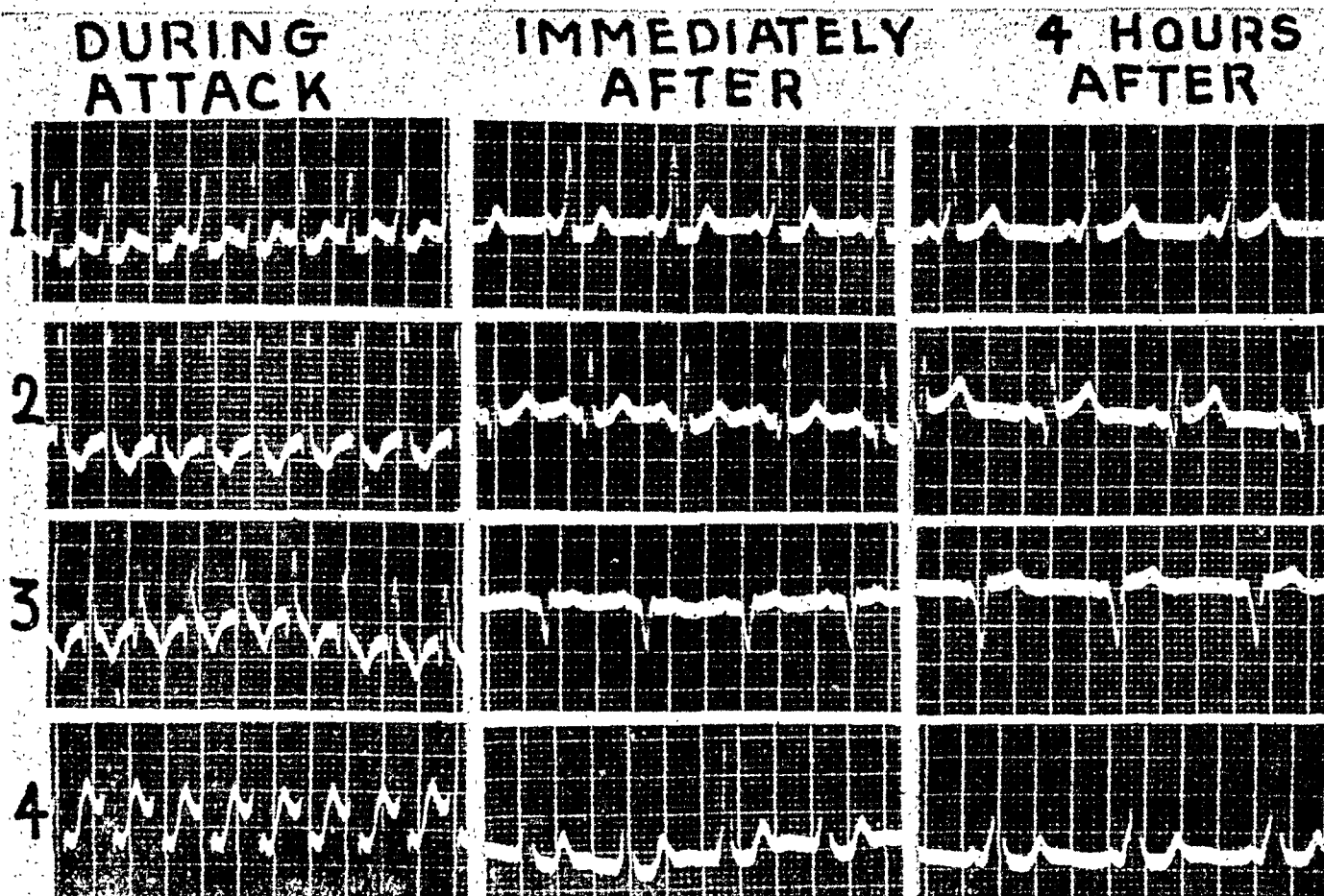


Fig. 1.—Electrocardiograms of the male parent during and after an attack of paroxysmal tachycardia. Note the shortened P-R interval and bizarre QRS complex characteristic of the Wolff-Parkinson-White syndrome during the period of normal sinus rhythm.

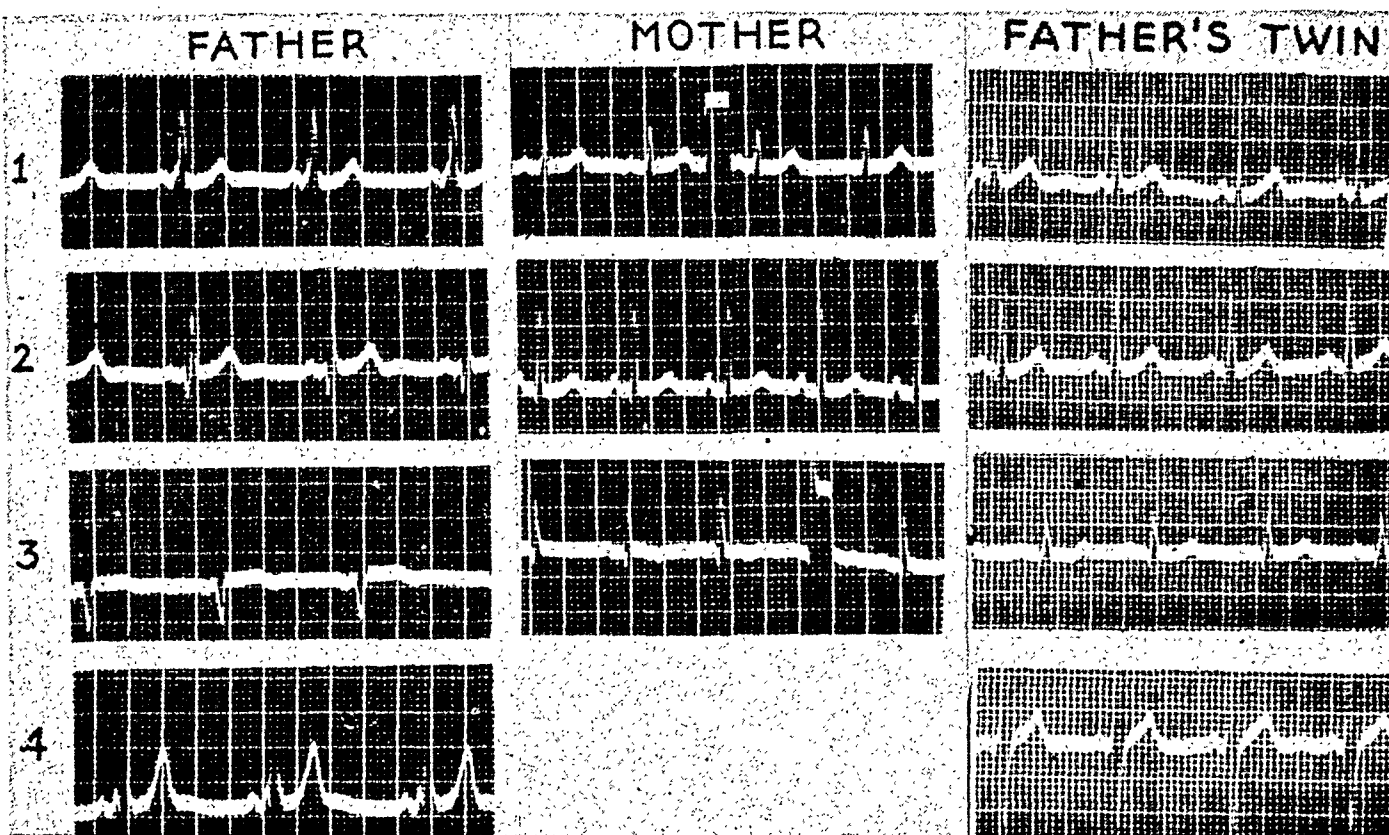


Fig. 2.—Compare the normal P-R intervals and normal QRS complexes in the female parent and the male parent's dizygotic twin with the shortened P-R interval and bizarre QRS complex of the male parent.

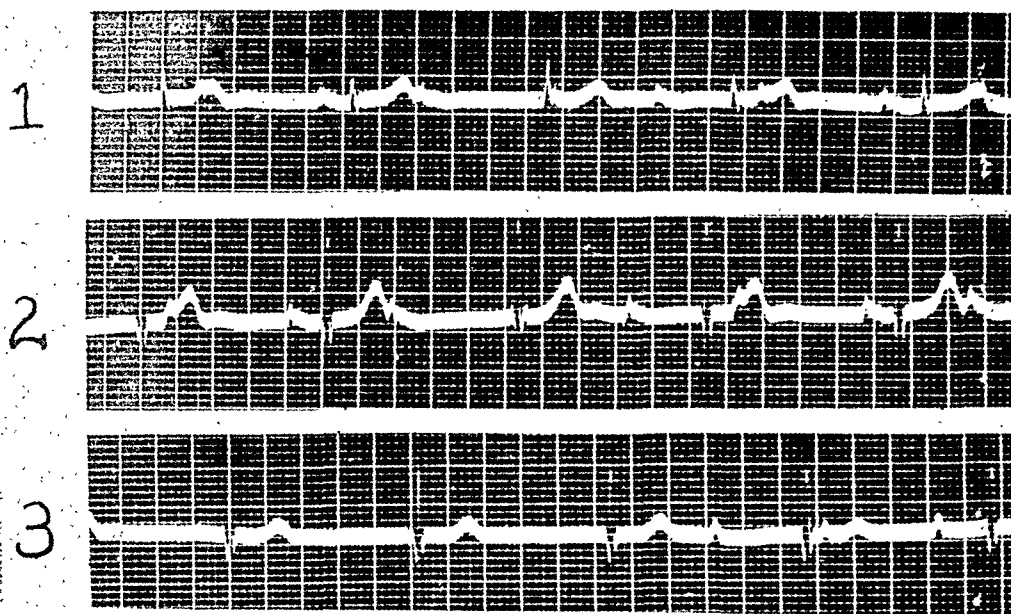


Fig. 3.—Electrocardiogram of the surviving sibling, showing the presence of complete A-V heart block with a ventricular rate of 60 per minute.

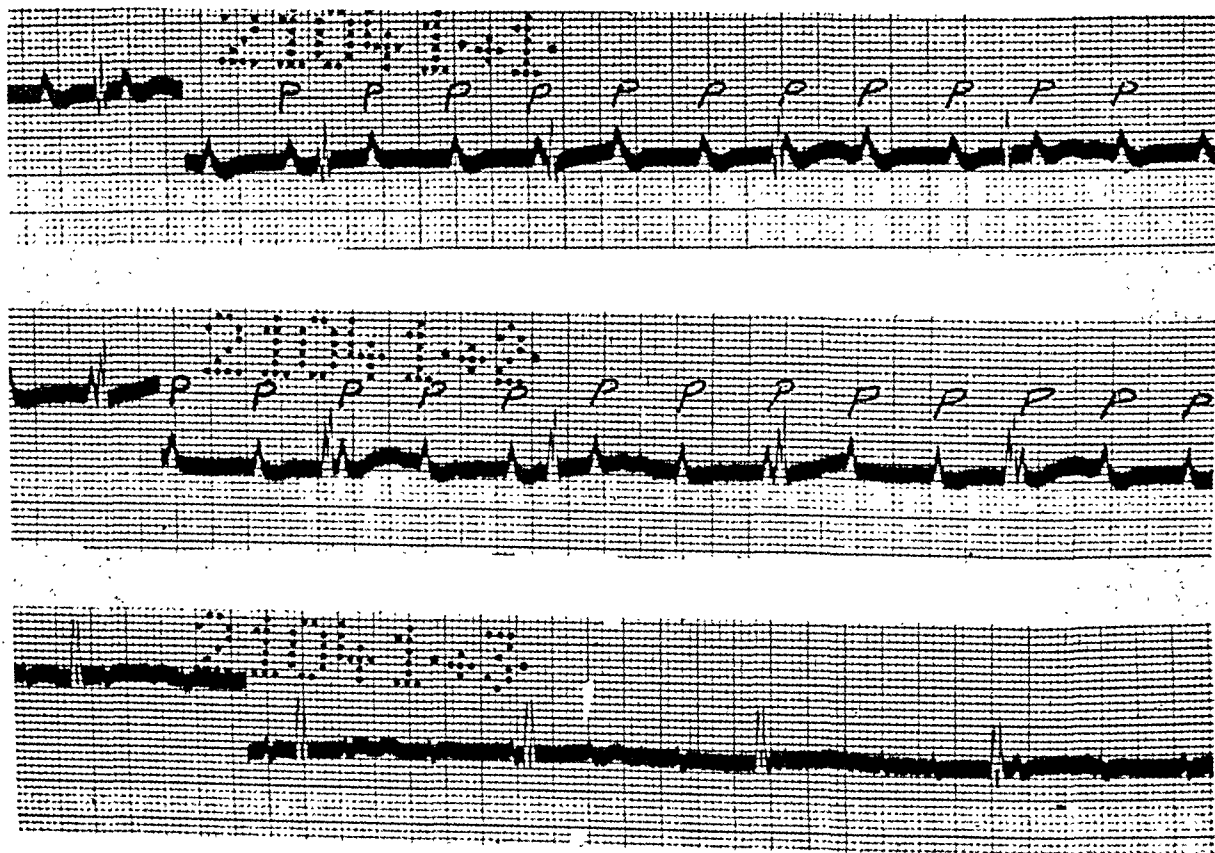


Fig. 4.—Electrocardiogram of the nonsurviving sibling showing the presence of complete A-V heart block, the ventricular rate being 50 per minute.

two years younger, has never shown evidence of a cardiac lesion and has remained in excellent health since his birth.

During the mother's third and last pregnancy, at which time she was 29 years of age, it was noted that the fetal heart rate was unusually slow and averaged approximately 50 beats per minute. An attempt to make an electrocardiogram of the fetus was unsuccessful. Delivery occurred at term and was uncomplicated. Immediately after birth the child showed no evidence of cardiac embarrassment but approximately thirty-six hours afterward, he became increasingly cyanotic and showed progressive respiratory difficulty. A loud systolic murmur became audible over the heart. The rate remained around 50. The child lived three days and died during an attack of respiratory distress. An electrocardiogram had been made about thirty hours before death and showed evidence of complete A-V heart block, with a ventricular rate of 50 per minute (Fig. 4).

The results of autopsy* findings are as follows: "The heart was slightly large, but its general configuration was normal. The ductus arteriosus which was widely patent was only slightly smaller in caliber than the pulmonary artery. There was a constriction in the distal portion of the aortic arch just proximal to the entrance of the patent ductus arteriosus" (Fig. 5). "The interior of the heart was normal, and the interventricular septum was intact. The heart and aorta weighed 40 Gm., and all the coronary vessels and the myocardium were normal. The section of muscle

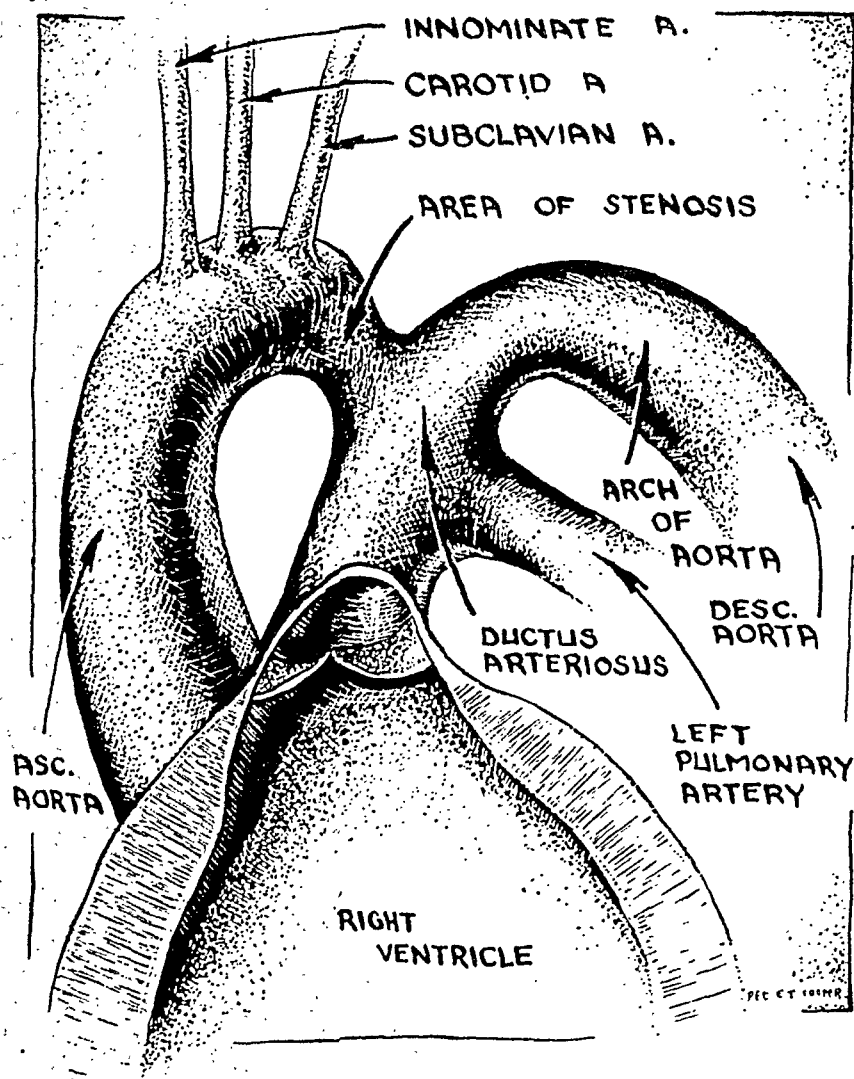


Fig. 5.—Schematic drawing of the anomalous vessels in the case of the nonsurviving sibling with congenital complete A-V heart block.

*Autopsy was performed by Dr. Edith L. Potter, at the University of Chicago Lying-In Hospital.

from this child's heart failed to show anything which could be identified as a bundle of His. However, the significance of this finding is questionable since at times it is impossible to identify this structure in normal hearts."

DISCUSSION

The diagnosis of congenital complete A-V heart block in the two siblings described in this report seems to be unquestionable, according to the criteria established by Yater.³ It should be pointed out, however, that in both instances there was no evidence of an associated interventricular septal defect, even though statistical studies indicate a high incidence of this anomaly in children with congenital heart block.⁴ It is also of interest that the male parent suffered from another type of anomalous conduction (Wolff-Parkinson-White syndrome), but in the absence of additional evidence it would be hazardous to suggest that any causal relationship exists between the two.

SUMMARY

1. Evidence is presented to indicate that familial congenital complete A-V heart block is a clinical entity.
2. The presence of an anomaly in conduction in one of the parents (Wolff-Parkinson-White syndrome) is briefly discussed.

REFERENCES

1. Aylward, R. D.: Congenital Heart Block, *Brit. M. J.* 1:943, 1928.
2. Aitken, J. K.: Congenital Heart Block, *Lancet* 2:1375, 1932.
3. Yater, W. M.: Congenital Heart Block, *Am. J. Dis. Child.* 38:112, 1929.
4. Schnitker, M. A.: *The Electrocardiogram in Congenital Cardiac Disease*, Cambridge, 1940, Harvard University Press.

Abstracts and Reviews

Selected Abstracts

Jaffe, Rudolf: Chronic Isolated Myocarditis. *Cardiologia* 10: 402, 1946.

In 5,000 autopsies in Venezuela, 500 cases of isolated myocarditis were found. Identifiable underlying heart disease was absent in all but two patients who showed Aschoff bodies. Clinically, heart failure and noncharacteristic electrocardiographic changes were present. The disease lasted months or years. Some patients died suddenly. On autopsy the hearts were enormously dilated, without hypertrophy (weight rarely over 400 grams), and flabby. The myocardium was cloudy, friable, and at times showed small scars. Mural thrombi were often present. Histologically, the myocardium showed infiltration with round cells, plasma cells, and eosinophiles. Focal or diffuse fibroblastic or granulomatous proliferations progressing to scars were found alone or in combination with cellular infiltration. This picture is identical with Fiedler's or the isolated myocarditis of the Americans.

Myocardial fibrosis is considered the end picture of diffuse inflammation. The author suggests a classification into specific (bacterial, rheumatic) and nonspecific myocarditis. In his series he found a striking coincidence with three other diseases: syphilis was present in 44 per cent, bilharziasis in 48 per cent, and necatoriasis in 28 per cent. The percentage incidence of these three diseases was much higher than in the patients of his series who did not have myocarditis. Some patients had other infectious diseases or beriberi.

All cases showed the same anatomicohistological picture. Further routine histologic examinations showed as early stages of the diseases focal fatty degeneration which is considered the visible expression of cellular damage. The later changes are a reaction to irritation or are a regenerative process. Thus, only the muscle damage is a direct consequence of the underlying disease; all other changes are secondary. The nature of the muscle damage is thought to be allergic, with nutritional factors superimposed. All the mentioned diseases produce muscle damage with antibody formation. In a subsequent injury, an allergic reaction occurs, producing the picture of myocarditis. Two different diseases may cause it; one may sensitize, the other may produce the allergic reaction.

LENEL.

Proger, S., and Dekamas, D.: Some Effects of Injected Cytochrome C in Myocardial and Cerebral Anoxemia in Man. *J. of Pediat.* 29:729 (Dec.), 1946.

Cytochrome C exists in organs in suboptimal amounts. Therefore, as there seems to be relatively more cytochrome oxidase present than is required for activation by the small amounts of cytochrome C present, it is reasonable to suppose that an added supply of cytochrome might be effective in combatting anoxemia. Material for testing this hypothesis was obtained by the Keilin and Hartree method of preparing cytochrome C. This material seems to be both nontoxic and stable. Four patients who showed marked electrocardiographic response following ten to twenty minutes exposure to an atmosphere containing 10 per cent oxygen and 90 per cent nitrogen were selected for this experiment. It was found that 60 mg. of cytochrome C given intravenously prevented these changes. The cerebral effects of anoxia, as measured by visual discrimination and code transliteration tests, could also be prevented by the same dose of cytochrome C.

The effects of cytochrome C were also tried clinically on four patients with angina pectoris, and found to be moderately effective in increasing the capacity for physical exertion. The effects of the continued daily administration of cytochrome C on Raynaud's disease and on patients with intermittent claudication were more striking and the benefits more marked. In acute myocardial infarction, no improvement was observed.

These experiments are of great interest and the results may be applicable to a great variety of conditions in which anoxia is of prime consideration. HAUB.

Muntz, H. H., Ritchie, J. O., and Gatch, W. D.: Adrenalin Producing Tumor (Pheochromocytoma) Containing 2,300 Milligrams of Adrenalin. Ann. Int. Med. 26:133 (Jan.), 1947.

A case of pheochromocytoma in both adrenal glands confirmed by necropsy is described. The patient, a 39-year-old woman, died while being operated on for removal of a right-sided adrenal tumor; the existence of which had been suspected during life because of spontaneous and induced crises of marked hypertension, along with x-ray visualization of a defect of the superior calyx of the pelvis of the right kidney, which was presumably due to a mass overlying the superior pole of the kidney. Induction of hypertensive crises during life had followed the intravenous administration of histamine acid phosphate or massage of the palpable tumor mass.

The significant findings at autopsy consisted of a well-encapsulated tumor of the right adrenal gland, about the size of an orange and weighing 350 grams; two spherical nodules in the medulla of the left adrenal gland, each measuring about 1 cm. in diameter; and a tumor of the thyroid gland with metastasis to the regional lymph nodes. Histologic examination of the bilateral adrenal tumors demonstrated in them the typical architecture of pheochromocytoma, whereas the cellular pattern of the tumor in the region of the thyroid gland and its regional lymph nodes was characteristically carcinomatous. By means of biologic assays of the single large pheochromocytoma, it was calculated that it contained 671 mg. of epinephrine for each 100 grams of tumor. This is equivalent to a total content of 2.35 grams of epinephrine, an amount estimated to be present, in physiologic proportions, in the adrenal glands of 31 cattle or 261 normal men.

WENDKOS.

Rosenbaum, F. F.: Right Ventricular and Right Auricular Hypertrophy of Obscure Origin. Ann. Int. Med. 26:76 (Jan.), 1947.

Two instances of idiopathic right ventricular hypertrophy and dilatation in adult women are described. Autopsy examination revealed, in one case, associated dilatation of the entire pulmonary arterial tree without disease of the pulmonary arterial walls, and in the other, dilatation of the right auricle and moderate hypertrophy of the left ventricle without any other significant finding. Recognizable congenital anomalies were not present. In both cases, the usual causes of cor pulmonale were excluded. The clinical features of the syndrome are also summarized. The constant occurrence of cyanosis and ascites in the disorder is noted. The electrocardiographic characteristics are also discussed, with attention directed specifically to the occurrence of right axis deviation and large, slightly delayed R waves in precordial leads derived from the right hemithorax. Reports of similar cases in the literature are thoroughly reviewed by the author. He accepts only six as being authentic and six others as probably authentic examples of the same syndrome.

WENDKOS.

Solomon, S., and Irwin, C. W.: Cutaneous Diphtheria with Toxic Myocarditis: Report of a Total Case With Necropsy Finding. Ann. Int. Med. 26:116 (Jan.), 1947.

A case of cutaneous diphtheria complicated by acute myocarditis is described. The sudden development of complete A-V heart block established the diagnosis of cardiac involvement during life. Microscopic sections of the ventricular myocardium, at autopsy, revealed scattered foci in which the myocardial fibers had disappeared leaving only stroma and a small infiltrate of lymphocytes, plasma cells, and macrophages. Bacteriologic study of the skin lesions had demon-

strated the presence of Klebs-Löffler bacilli, virulent to nonprotected guinea pigs, in pure culture. Because of their experience with this case, the authors emphasize the need for early and adequate treatment with diphtheria antitoxin whenever cutaneous diphtheria is suspected.

WENDKOS.

Bushong, B. B.: Traumatic Rupture of the Aortic Valve: Report of Two Cases, One a Proved and the Other a Probable Example of This Condition. *Ann. Int. Med.* 26:125 (Jan.), 1947.

Two cases of musical diastolic murmurs, presumably due to traumatic rupture of the aortic valve, are reported. One was a 50-year-old man who had apparently been in good health until he developed chest pain and dyspnea while attempting to extricate himself from a truckload of fence posts which had knocked him down. Sixty-nine days after this injury, he died of progressive cardiac failure. The autopsy revealed a transverse tear along the right anterior and posterior aortic valve leaflets which allowed the cusp margins to prolapse into the ventricle. Although no associated disease of the aortic valve or aorta was described, the weight of the heart was increased to 600 grams and hypertrophy and dilatation of both ventricles and auricles were present.

The other case was that of an 11-year-old boy who was not suffering from symptoms of cardiac failure but was examined because of the sudden development of a buzzing sound in the chest which presumably followed a blow to the chest during a boxing lesson. No other murmurs were audible. Peripheral signs of aortic incompetency were well pronounced. No history of rheumatic fever could be obtained. The electrocardiogram was normal. A sound tracing showed the typical pattern of the "cooing-dove" murmur.

WENDKOS.

Robbins, L. L.: The Technique of the Roentgenologic Demonstration of Pulmonary Infarct. *Am. J. Roentgenol.* 56:736, 1946.

The importance of early diagnosis of pulmonary infarct has become more evident with the institution of modern therapeutic methods for preventing and combating the sequelae of infarction.

Approximately 75 per cent of infarcts occur in the lower portion of the lung. The size of the infarct may vary from a small linear lesion lying against the pleura to a large lesion occupying the greater portion of a lobe. The shape of the infarct is dependent on its location, but it is always peripheral with its long axis parallel to the pleura. The shadow as a rule has a curved proximal margin. The infarct is at first indistinct but gradually becomes more sharply defined. In a period varying from days to a month it assumes a linear shape and may finally disappear except for a very fine linear scar.

At least two views, a posterior-anterior and a lateral view of the chest, is the minimal number of films necessary to demonstrate adequately an infarct. If the condition of the patient permits, roentgenoscopy of the chest is very helpful. Adequate evaluation of the thoracic dynamics and optimum position for making films is possible following roentgenoscopy. Spot films during fluoroscopy frequently will better demonstrate infarcts than a full 14x17 film.

The author has found that the Merrill modification of the Fuch's technique, using a high optimum kilovoltage and varying the milliampere seconds with the size of the patient, has resulted in a film of more uniform quality. A roentgen differential diagnosis is included in the paper.

ZION.

Lindgren, E.: The Roentgen Diagnosis of Arteriovenous Aneurysm of the Lung. *Acta radiol.* 27:585 (No. VI), 1946.

The author stresses the distinction, first made by Reid in 1925, between congenital arteriovenous aneurysm and acquired arteriovenous fistula. The congenital lesions have not been found to enlarge the heart, regardless of their proximity to it. Three cases of arteriovenous aneurysm of the pulmonic vessels are reported in addition to the two in the literature.

The salient clinical characteristics were a systolic bruit over the aneurysm, heard through the chest wall; clubbed fingers; cyanosis of varying severity; normal heart size; and a characteristic roentgen picture of a nonpulsatile density, with vascular markings communicating with

it, in the lung field. The density becomes larger during the Valsalva and smaller during the Müller experiments. Body section films and angiocardiology were helpful in the differential diagnosis. The most common clinical complications, in addition to poor exercise tolerance, were hemoptysis and syncopal or focal cerebral manifestations of transitory nature attributed to air embolism.

Case 1, a 30-year-old man, had an arteriovenous aneurysm in the left chest, and a presumably unrelated mitral stenosis. By oxygen saturation studies, the author estimated that 28 per cent of the pulmonary blood was short-circuited through the communication. Case 2, a 29-year-old man, had hereditary hemorrhagic telangiectasis with multiple lung arteriovenous aneurysms and many blue-black dots scattered over his skin representing smaller lesions. The two largest pulmonary aneurysms were close together in the right lung field, over which a systolic bruit could be heard. The heart was normal. Case 3, a 25-year-old man, had a left lower lobe aneurysm which caused frequent small hemoptyses. He had been thought to have congenital heart disease or pulmonary tuberculosis during his twelve years of symptoms. The arterial oxygen saturation was 83.8 vols. per cent after fifteen minutes of 100 per cent oxygen. There were no evidences of a cardiac lesion.

The two largest aneurysms in Case 2 and the left lower lobe lesion in Case 3 were successfully resected by Crafoord. A continuous thrill and definite systolic pulsation could be felt in the exposed aneurysms. Cyanosis disappeared after the operation and the immediate convalescence was satisfactory in both cases. Heart volume of both patients increased slightly following the resections.

SAYEN.

Broch, O.: The Electrocardiogram in Derangements of the Organism's Water and Electrolyte Metabolism. Acta Med. Scandinav. 126:157 (Nos. II-III), 1946.

The literature relative to electrocardiographic change associated with calcium, potassium, and acid-base imbalance is reviewed, as well as that on dehydration, acute hemorrhage, and traumatic and anaphylactic shock. The author emphasizes that the RS-T segment changes associated with fluid and electrolyte disturbances are well known, but since the two generally occur together, it is not established whether lowered coronary blood flow or the effect locally on the heart muscle of change in metabolites is responsible for these changes.

Electrocardiograms of 13 cases of severe dehydration were taken before and during treatment. The series included cases of acidosis, alkalosis, gastroenteritic diarrhea, shock, asphyxia, and pyloric or lower small intestinal obstruction. They had in common an electrocardiographic picture of RS-T segment depression (one to four mm.) usually greater in Leads II, III, and CF₄ than in Lead I. The height and sharpness of the T waves were sometimes increased. The RS-T segment depressions vanished in every case immediately after the administration of one or two liters of normal saline intravenously and did not return, although the chemical imbalances had not yet been corrected. The T waves often remained low for a few days to three weeks thereafter and there was sometimes a prolongation of the Q-T interval. Routine chemical studies included total base, CO₂ and hemoglobin determinations, and usually serum chlorides. The author believes the electrocardiographic changes were due to diminished blood volume with secondary reduction of coronary arterial flow and not to disturbances in chemical equilibrium.

An additional part of the study was the administration of potassium salts to four uremic patients with elevated serum potassium levels. All developed further increase in serum potassium and the T-wave height increased in their electrocardiograms (inverted T waves becoming less inverted). The Q-T interval did not change.

SAYEN.

Biorek, G.: Five Cases With Pre-Excitation Electrocardiograms. Acta Med. Scandinav. 125:465 (No. V), 1946.

Of five cases of pre-excitation, two showed a short P-R interval; slurred upstroke of QRS complex, and attacks of paroxysmal tachycardia typical of the Wolff-Parkinson-White syndrome. Change of position and a sympathomimetic drug influenced the pattern considerably in one of these cases. The other three cases had P-R intervals of 0.12 second or more, but a deformity of the upstroke of QRS in various leads and an abnormal RS-T segment and T-wave pattern, which

in two cases involved only Leads II and III. The tracing changed at times to the abnormal pattern during exercise or amyl nitrite inhalation, but at other times the abnormal pattern appeared and disappeared spontaneously. One case showed two abnormal patterns. The author's Figs. 4C and 3B are particularly interesting examples of the change of abnormal RS-T segments and T waves in Leads II and III to normal; in one case spontaneously, and in the other after exercise.

Three of the cases had mitral stenosis. All five had normal cardiac function on exercise tests. It is emphasized that pre-excitation is associated rather frequently with organic heart disease but its prognostic significance remains uncertain. SAYEN.

Trier, M.: Penicillin Treatment of Subacute Bacterial Endocarditis. *Acta Med. Scandinav.* 126:140 (Nos. II-III), 1946.

The author reports four cases and reviews the literature in part. Two patients were "cured" (five and nine month follow-ups). The two fatalities were thought at necropsy to have resulted from cardiac failure, although in one case there was still slight bacterial activity deep in the vegetations. Three to six weeks of therapy with 200 to 300 thousand units of penicillin daily is considered adequate for most cases. Since only small quantities of the drug are available in Denmark the author recommends that it be reserved for patients who do not have signs of advanced heart damage, particularly failure associated with aortic valve destruction, in order to minimize the number of those who die of congestive failure after a bacteriologic "cure."

SAYEN.

Altschul, Rudolf: Experimental Cholesterol Arteriosclerosis. *Arch. Path.* 42:277 (Sept.), 1946.

The writer was the first to study the reaction of skeletal muscle to experimental cholesterol arteriosclerosis. Rabbits, guinea pigs, and golden hamsters were placed on a diet of powdered egg yolk and yeast to produce an ample degree of experimental cholesterol arteriosclerosis. Three types of changes were noted in skeletal muscle: (1) waxy hyaline degeneration of the sarcoplasm; (2) basophilic granular degeneration of the sarcoplasm with infiltration of calcium salts in which the muscle nuclei did not disappear, but were liberated from the diseased sarcoplasm and were sufficiently proliferated to form a distinctive accumulation of cells; and (3) a survival of basophilic sarcoplasm, but with the fibers remaining very thin and the nuclei proliferating in longitudinal nuclear rows.

Altschul admits that none of the above changes are specific for experiments with cholesterol feeding, since they occur under many circumstances, the most important of which may be regarded as nutritional myodegeneration. There is one change in skeletal muscle which he regards as specific for cholesterol arteriosclerosis; namely, transformation of muscle nuclei into foam cells. He points out that foam cells have never been found in skeletal muscle except under conditions of experimental cholesterol arteriosclerosis. He also states that these new proliferated nuclei show a distinct phagocytic activity and that the associated vascular change, lipid arteriosclerosis, is not directly connected with the changes in the skeletal muscle fibers. The vascular changes, per se, apparently cause no damage to the muscle tissue proper. GOULEY.

Walser, A.: The Influence of Autonomic Drugs on the T Waves in the Exercise Electrocardiogram. *Cardiologia* 10:231, 1946.

The author studied the effect of exercise on the T-wave patterns of ten athletes. He found, as had other investigators, that mild exercise was followed immediately by lowered T-wave amplitude which gave way in about five minutes to a longer period of increased amplitude before the height returned to normal. Violent exercise (eight flights of stairs) caused a reversal of this order, an immediate elevation of the T waves being followed by a period of subnormal amplitude. The latter type of response was said to occur with light exercise when the subjects were poorly trained or neurasthenic.

The effect of synephrin tartrate (60 mg.) plus atropine sulfate (1.0 mg.) was to exaggerate the usual response to violent exercise in the electrocardiogram. A combination of physostigmine salicylate (1.0 mg.) and ergotamine tartrate (0.5 mg.) reduced the amount of T-wave flattening somewhat. The author believes that the effect of an increase of sympathetic tone was to reduce and the effect of increased vagal tone to increase the T-wave amplitude, at least in the post-exertional phase in athletes undergoing violent exercise. LENEL.

Reveno, W. S.: Thiouracil in Angina Pectoris. *Am. J. Medicine* 1:607 (Dec.), 1946.

Eight patients with angina pectoris were given an initial daily dose of 0.6 to 0.4 Gm. of thiouracil until some improvement was noted. The dose was then reduced to 0.3 to 0.2 Gm. daily. Nitroglycerin and sedatives were permitted as needed. The basal metabolic rate was determined at two-week intervals at first, and later at four-week intervals.

In two patients who failed to remain under observation for longer than six weeks and three months, respectively, no improvement was noted. A third patient, observed for two months, reported improvement. In these three patients the reduction in basal metabolic rate varied between —3 and —14 per cent.

The remaining five patients, who were observed for six to eight months, usually demonstrated improvement in symptoms by the end of the second month of treatment. The drop in the basal metabolic rates of these patients varied between 7 and 29 per cent.

Two patients developed symptoms and signs of myxedema. Another patient developed joint pains and headache on the sixth day of treatment, which necessitated temporary interruption of therapy for one week. Upon resuming the drug at a reduced dosage level no further difficulty was experienced until the eighth month when the thyroid became diffusely enlarged. A fourth patient experienced temporary gastric distress.

Substitution of 75 to 125 mg. of propyl-thiouracil in one patient did not satisfactorily maintain the improvement that had been obtained with thiouracil. However, two patients were successfully maintained on 100 mg. of propyl-thiouracil for three months, after improvement had been obtained on thiouracil.

After cessation of thiouracil four of five patients remained improved for one to four months. No changes occurred in the electrocardiograms of any patient while on thiouracil.

FRIEDLAND.

Scarlini, F.: Rupture of a Chronic Fibrous Aneurysm of the Interventricular Septum
Cuore e Circ. 30:89 (July-August), 1946.

A clinical case is reported where a chronic fibrous aneurysm of the interventricular septum due to coronary heart disease ruptured into the right ventricle. The patient, a 71-year-old woman, suddenly complained of precordial pain and appeared to be in shock. Low grade fever, leucocytosis, and an increased sedimentation rate were noted. A loud systolic murmur and a systolic thrill were present over the precordium. The electrocardiogram showed high P waves in Lead II and general signs of coronary heart disease. The x-ray revealed an enlargement of the cardiac silhouette with displacement of the lower right arch (enlargement of the right ventricle) and deformity of the left border with absence of pulsations near the apex.

The clinical diagnosis was that of recent infarction with subsequent rupture of the interventricular septum. Death occurred twelve days later. The autopsy showed that no recent infarction existed but that a recent perforation of a very fibrotic septum had occurred. The author considers that the absence of typical changes of acute infarction in the electrocardiogram should permit a correct diagnosis when the clinical picture is that of rupture of the septum.

LUISADA.

Castleman, B., and Bland, E. F.: Organized Emboli of the Tertiary Pulmonary Arteries.
Arch. Path. 42:581 (Dec.), 1946.

The authors report a case of a white woman, 44 years of age, who, following pregnancy nine years before, became progressively cyanotic. At the age of 36 she had sharp intermittent pain

substernally and in the epigastrium, lasting from a few minutes to several hours; soon thereafter she developed effort dyspnea. Examination at that time revealed orthopnea, some cyanosis without clubbing of the fingers. There were no heart murmurs, but the second pulmonic sound was loud, and right axis deviation and large P waves were seen in the electrocardiogram. Fluoroscopically, there was enlargement of the right ventricle and pulmonary conus without auricular enlargement. The patient developed progressive right heart failure with venous distention, enlargement of the liver, and leg edema. The lungs remained clear throughout the entire illness. Acute general peritonitis was the terminal event.

Necropsy revealed marked dilatation and hypertrophy of the right auricle and ventricle, with a small left ventricle. The coronary arteries and the aorta were normal. In contrast, the pulmonary artery showed marked atherosclerosis of all of its main branches, with occlusion in all tertiary branches by tough fibrous trabecular formations attached to the intima and associated with thrombosis in various stages of organization. There was marked elastosis in the walls of these occluded branches and also in the trabecular channels filling the lumina. Distal to these points of occlusion, the walls of the small branches of the pulmonary artery were normally thin and completely free from atheroma. The picture was that of organized and recanalized thrombi. The interesting thing in this case, different from all other reported cases of pulmonary arteriosclerosis, was the fixed and predictable site for the development of occlusion. Small pleural fibrous plaques were present which were believed to be the result of previous infarctions. The veins of the legs and pelvis were not examined.

It is the belief of the writers that the widespread obstruction in the tertiary branches was the result of some previous pelvic operation, with pelvic vein thrombosis and a secondary shower of emboli throughout the lungs but with lodgment sufficiently proximal to the pleura to allow collateral circulation to function and develop, thus preventing infarction in the mid- and central portions of the lungs.

GOULEY.

Wheeler, E. O., Bridges, W. C., and White, P. D.: Diet Low in Salt (Sodium) in Congestive Heart Failure. J.A.M.A. 133:16 (Jan. 4), 1947.

The mechanism of the production of edema in heart failure may be dependent on several factors, such as the retention of sodium, increased hydrostatic pressure, and, in some cases, a decrease in colloid osmotic pressure due to low serum proteins. Of these, the retention of sodium is one of the most important and at the same time one of the easiest to treat.

The regimen adapted was a low sodium diet (1.5 to 2.0 Gm. per day) which yielded a neutral ash. Fluids were allowed as desired up to 3 liters per day. Most of the patients were given ammonium chloride, mercurial diuretics, and digitalis as required.

Fifty patients were selected in whom previous treatment had yielded unsatisfactory results; either their dyspnea and edema were not controlled, or the control of these symptoms required the use of mercurial diuretics at too frequent intervals. The duration of treatment ranged from one month to one and a half years; the average was seven months.

Four of the patients were unable to follow the diet satisfactorily. The remainder cooperated and maintained a satisfactory restriction of sodium. In eleven patients the results could not be evaluated for various reasons. Of the remaining thirty-five patients, twenty-two showed improvement. Eighteen of twenty patients with hypertensive and/or coronary heart disease showed improvement, and in nine of these the improvement was marked. Of the four remaining patients whose heart disease was of miscellaneous etiology, three showed improvement. In general, patients with coronary and hypertensive heart disease responded much better than did patients with rheumatic heart disease.

These authors advocate the more widespread use of the sodium diet in the treatment of congestive failure.

BELLET.

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

MEMBERSHIP.

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members resident in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....	\$ 2.50	Contributing Membership.....	\$25.00
Journal Membership.....	\$10.00	Patron Membership.....	\$50.00 or more

The dues of the local Heart Associations are added to these.

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*.

Journal Membership includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the AMERICAN HEART JOURNAL through the publishers does not provide for membership in the American Heart Association.

OFFICERS

Vice-President
DR. ARLIE R. BARNES

President
DR. HOWARD F. WEST

Secretary
DR. HOWARD B. SPRAGUE

Treasurer
DR. GEORGE R. HERRMANN

Acting Executive Secretary
DR. H. M. MARVIN

Acting Medical Director
DR. DAVID D. RUTSTEIN

DIRECTORS

DR. EDGAR V. ALLEN.....Rochester, Minn.
DR. GRAHAM ASHER.....Kansas City, Mo.
*DR. ARLIE R. BARNES.....Rochester, Minn.
DR. ALFRED BLALOCK.....Baltimore
*DR. WILLIAM H. BUNN.....Youngstown, Ohio
DR. CLARENCE DE LA CHAPELLE.....New York City
*DR. TINSLEY R. HARRISON.....Dallas
DR. GEORGE R. HERRMANN.....Galveston
DR. T. DUCKETT JONES.....Boston
DR. LOUIS N. KATZ.....Chicago
DR. SAMUEL A. LEVINE.....Boston
DR. GILBERT MARQUARDT.....Chicago
*DR. H. M. MARVIN.....New Haven
*DR. EDWIN P. MAYNARD, JR.....Brooklyn
*DR. THOMAS M. McMILLAN.....Philadelphia
DR. JONATHAN MEAKINS.....Montreal, Can.
DR. E. STERLING NICHOL.....Miami

DR. HAROLD E. B. PARDEE.....New York City
DR. WILLIAM B. PORTER.....Richmond, Va.
*DR. DAVID D. RUTSTEIN.....New York City
*DR. JOHN J. SAMPSON.....San Francisco
DR. ROY W. SCOTT.....Cleveland
*DR. HOWARD B. SPRAGUE.....Boston
DR. GEORGE F. STRONG.....Vancouver, B. C., Can.
DR. WILLIAM D. STROUD.....Philadelphia
DR. HOMER F. SWIFT.....New York City
DR. WILLIAM P. THOMPSON.....Los Angeles
DR. HARRY E. UNGERLEIDER.....New York City
*DR. HOWARD F. WEST.....Los Angeles
DR. PAUL D. WHITE.....Boston
DR. FRANK N. WILSON.....Ann Arbor
*DR. IRVING S. WRIGHT.....New York City
DR. WALLACE M. YATER.....Washington, D. C.

*Executive Committee.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

Vol. 34

AUGUST, 1947

No. 2

Original Communications

THE CLINICAL SYNDROME ASSOCIATED WITH PULMONARY ARTERIOVENOUS FISTULAS, INCLUDING A CASE REPORT OF A SURGICAL CURE

HOWARD B. BURCHELL, M.D.,* AND O. THERON CLAGETT, M.D.†
ROCHESTER, MINN.

WHEN a young person presents himself for medical examination with cyanosis, clubbing of the fingers and toes, and polycythemia, the most common etiological condition is congenital heart disease. That such a picture may be associated with an arteriovenous shunt in the lesser circulation has become of increased diagnostic importance, for, with the recent advances in the field of thoracic surgery, complete cure of the condition may be effected with minimal operative risk. The relationship between polycythemia and a pulmonary arteriovenous shunt was first clearly elucidated by Hepburn and Dauphinee,¹ in 1942, in a case in which the patient was cured by pneumonectomy.‡ The first case in which a clinical diagnosis was made was reported by Smith and Horton² in 1939. Previous to these first clinical studies, there had been anatomic descriptions of the pulmonary lesions following post-mortem examinations by Churton,³ Wilkens,⁴ and Rodes.⁵ The case recorded by Churton contains few data and is mainly of interest in that seven lesions, apparently arteriovenous varices, were present. Wilkens' case was that of a 23-year-old woman who died of an intra-thoracic hemorrhage. Excellent clinical and pathologic data are available. Three lesions were present and there were the additional findings of a patent foramen ovale and bilateral apical tuberculosis of the lungs. Rodes presented the earliest pathologic study in which the pulmonary lesions were definitely associated with the pre-mortem picture of cyanosis and polycythemia.

Received for publication Oct. 21, 1946.

*Division of Medicine, Mayo Clinic.

†Division of Surgery, Mayo Clinic.

‡Carried out by Janes and Shenstone.

Bower's⁶ case, in which an infant died from an intrathoracic hemorrhage the day after birth, is of interest in indicating that the dilated sinusoidal vessels are part of the congenital defect and that cyanosis may not be noticeable at birth.

It was the successful surgical treatment in Hepburn and Dauphinee's case that placed emphasis on the curability of polycythemia associated with pulmonary arteriovenous fistula; similar cases, with cure by pneumonectomy, have been reported by Jones and Thompson⁷ and Adams, Thornton, and Eichelberger.⁸ Janes⁹ reported a case with surgical cure in which local excision of three hemangiomas was carried out. Additional cases emphasizing the clinical syndrome as an entity have been described by Goldman¹⁰ and by Makler and Zion.¹¹ A report of a very carefully studied patient with post-mortem examination has been published by Sisson, Murphy, and Newman.¹² The rarity of the condition is apparent from the fact that the extensive review of the pathologic conditions of the pulmonary circulation by Brenner¹³ and reviews of the aneurysms of the pulmonary artery by D'Aunoy and van Haam¹⁴ and by Boyd and McGavack¹⁵ do not contain any references to pulmonary arteriovenous aneurysm.

Since arteriovenous fistulas in the systemic circulation present a well-known syndrome, it is worth while to compare the picture with that of a pulmonary arteriovenous fistula. Among the like effects, or similarities, one might expect the bruit, the increases of the cardiac output and the blood volume, and the dilatation of the vessels proximal to the fistula. Among the reversed or unlike effects, one would expect in cases of pulmonary fistula a high content of reduced hemoglobin in the arterial blood instead of a high content of oxyhemoglobin in the venous blood and a collapsing pulse in the hilar vessels instead of a collapsing pulse in the systemic arteries. Among the new effects, there could be predicted the effect of arterial hypoxemia, polycythemia and its consequent symptoms, hemoptysis, and the potentiality of arterial emboli from venous thrombosis.

In a case of pulmonary arteriovenous fistula it will be apparent that, since some of the blood, pumped into the pulmonary artery, will pass directly through the fistula without oxygenation, two primary circulatory faults result. The first is that the effective pulmonary flow is decreased and the second is that a mixture of venous and arterial types of blood, with a resultant arterial blood with incompletely saturated hemoglobin, is pumped into the aorta. These two conditions are those which are also present in cyanotic congenital heart disease. One might thus expect that the clinical picture of a large pulmonary arteriovenous fistula would simulate that of congenital heart disease, a tetralogy of Fallot, the severity of the symptoms in each instance being mainly dependent on the reduction of effective pulmonary flow.

An analysis of the symptoms and signs in the reported cases of pulmonary arteriovenous fistula reveals a stereotyped syndrome (Table I). The basic picture is one of cyanosis, clubbing of the fingers and toes, and polycythemia without abnormality of the heart. Dyspnea, dizziness, faintness, and thickness of the speech are common secondary symptoms. More than one-half the patients have had small capillary hemangiomas of the skin or mucous membranes. A bruit over the lung may or may not be discovered and, when present, it may or

TABLE I. SYMPTOMS AND SIGNS IN CASES OF PULMONARY ARTERIOVENOUS FISTULA

	AGE (YR.)	CYANOSIS	CLUBBING	DYSPNEA	HEMOPTYSIS	BRUIT	CARDIAC ENLARGEMENT	POLYCYTHEMIA	INCREASED BLOOD VOLUME	ARTERIAL HEMOGLOBIN (%)	ROENTGENOGRAM	LESIONS	REMARKS
Wilkins, ⁴ 1917	23	+		+	+	+	+				+	3	Fatal hemorrhage; necropsy
Rodes, ⁵ 1938	25	+	+	+	+	0	0	+			+	3	Fatal hemoptysis; necropsy
Smith and Horton, ² 1939	46	+	+	+	0	+	0	+	+		+	1	Living, 1946
Hepburn and Dauphinee, ¹ 1942	23	+	+	+	0	0	0	+	+	73	+	1	Pneumonectomy
Goldman, ¹⁰ 1943	22	+	+	+	0	0	0	+	+	70	+	1	
Adams and co-workers, ⁸ 1944	24	+	+	0	+	0	0	+	+	71	+	2	Pneumonectomy
Jones and Thompson, ⁷ 1944	24	+	+	0	0	+	0	+			+	1	Pneumonectomy
Janes, ⁹ 1944	30	+		0	+	+	0				+	3	Local excisions
Sisson and co-workers, ¹² 1945	45	+	+	+	+	+	+	+			+	2	Necropsy
Makler and Zion, ¹¹ 1946	20	+	+	+	0	+	0	+			+	4	
Present case	20	+	+	0	0	+	0	+	+	74	+	1	Lobectomy; well

may not have the continuous characteristics of systemic arteriovenous bruits. It may be of increased loudness in inspiration and practically inaudible on expiration. Cardiac enlargement has been present in only two cases. Its absence in other cases has been attributed to the small increase of cardiac work caused by the pulmonary arteriovenous fistulas.

The laboratory investigation has consistently revealed the presence of polycythemia, erythrocytes numbering between 6,000,000 and 8,000,000 per cubic millimeter of blood, and the hematocrit varying from 60 to 80 per cent erythrocytes. In all five cases in which the blood volume was determined it was increased to approximately twice normal value; splenomegaly, however, has been present in only two instances. The arterial hemoglobin saturation has been studied in only four cases. The fact that the percentages of the hemoglobin oxygen saturation of the arterial blood are nearly identical cannot be regarded as fortuitous. Rather it must be related to a compensatory process in the circulation, in which the arterial oxygen tension is held to a certain level by increased cardiac output. Increase of cardiac output, without parallel increase of oxygen consumption, will increase venous oxygen tension; the blood in the pulmonary artery will be less unsaturated and hence the shunted blood will have less effect in reducing the arterial hemoglobin saturation. These observations indicate that the stimulus for increased cardiac output is present until the arterial oxygen tension is approximately 40 mm. of mercury and correlate quite well with the reports indicating that cardiac output does not begin to increase under conditions of lowered oxygen pressure until the arterial oxygen tension drops to 45 to 50 mm. of mercury.¹⁶

In all the reported cases roentgenologic examination of the thorax has shown positive findings which may be practically diagnostic. A nodular-appearing lesion, often well shown by tomography, with pulsation when observed roentgenoscopically, and increased hilar pulsation on the side of the lesion, is the most characteristic picture. The importance of the roentgenologic examination lies not only in the diagnosis of the syndrome itself, but also in the determination of the number of lesions, for the fistulas are more likely to be multiple than single. In any plan for a surgical procedure the proper assessment of the number and size of various fistulas is of the utmost importance.

REPORT OF CASE

A college sophomore, 20 years of age, was referred to the Mayo Clinic for consideration of surgical treatment for a cyanotic disorder of the circulation.

The history, as obtained from the parents, was that the patient had been a normal-appearing baby at birth, that his development had been normal, and that it was not until he was about 8 years of age that the color of his lips was noted to be darker than that of other children. The teachers in grade school first noticed the clubbed fingers, and he complained of aching pains in the legs about this time. His early school years were uninterrupted and his scholastic record was excellent. He did not take part in school sports because of awkwardness and general inaptitude; he denied that he had shortness of breath. In recent years only after climbing three flights of stairs had he noticed shortness of breath. In recent years also he had occasional mild giddy spells with tinnitus, and, rarely, he noticed a mild frontal headache. There were no visual disturbances. For the past two years there had been an increasing amount of pain in the knee

joints and, beginning sixteen months previously, a superficial weeping ulceration of both ankles had developed. In 1941 he had an attack of "pleurisy" and was away from school three weeks.

On physical examination the most outstanding finding besides the cyanosis was the extensive clubbing of the fingers and toes and the enlargement of the wrist, knee, and ankle joints. His height was 6 feet, 2½ inches (189 centimeters), and his weight was 150 pounds (68.0 kilograms). The conjunctiva was congested and examination of the fundi revealed the retinal veins to be large, deeply cyanotic, and congested in appearance.

Examination of the heart revealed a forceful apical impulse in the midclavicular line and normally loud first and second sounds. There were no murmurs. On auscultation of the thorax over a small area below the right nipple there was a late systolic bruit, which varied in intensity, depending on the phase of respiration, being loudest in midinspiration (Fig. 1).

The spleen was enlarged and palpable at the costal margin. On the medial side of both ankles there was an area of red, moist, very superficial ulceration, similar to the stasis lesions of adults who have varicose veins and venous insufficiency of long duration.

Roentgenologic Data.—The thoracic roentgenogram showed an irregular nodular shadow in the right lung and a normal cardiac contour. Roentgenoscopic examination showed an irregular nodular pulsating mass contiguous to the inferior portion of the right hilus. The appearance was that of vascular abnormality. It was possible to obtain the thoracic roentgenogram that had been taken eight years previously when the patient was 12 years of age, and the appearance is similar (Figs. 2 and 3). On completion of the roentgenographic studies it was thought that the lesion might be confined to the right middle lobe.

The laboratory findings were confirmatory of the diagnosis of a pulmonary arteriovenous fistula (Table II).

Surgical Exploration.—In planning the surgical approach, it was hoped that right middle lobectomy might be possible, but in the event that this was impossible, or if the right middle lobe was not the site of the vascular abnormality, pneumonectomy was to be attempted. In order to measure the volume of the pulmonary arteriovenous shunt, it was planned at operation to take samples of blood simultaneously from a branch of the pulmonary artery and the radial artery. Additional samples were to be obtained from the superior pulmonary vein, if possible, or from the radial artery after the shunt was closed.

Exposure was obtained by an incision around the right scapula and resection of a long segment of the sixth rib. There were no pleural adhesions except between the middle lobe and the thoracic wall, where there were many tortuous vessels apparently communicating with the pulmonary circulation. Both the internal mammary artery and veins were several times normal size. There was a palpable thrill over the middle lobe. Dissection was carried down into the hilus and a large vessel, ostensibly a greatly dilated pulmonary artery to the middle lobe, was isolated, a specimen of blood was taken, and the vessel was ligated. Dissection of the hilus was continued, and when connections to the lobe were severed, it became apparent that a large quantity of blood was entering the lobe from the collateral vessels in the thoracic wall. The lobe became more and more congested. Separation of the lobe from the thoracic wall was accompanied by severe bleeding, and for a time it appeared as if the patient might die on the table from hemorrhage. The hemorrhage was finally controlled by mattress sutures, multiple ligatures, and oxidized cellulose gauze soaked in thrombin. The thorax was closed after the lung had been inflated, two catheters being inserted in the thorax for temporary closed drainage.

During the latter part of the operation, the patient received 7 liters of blood, 1 liter of which was his own blood which had been removed in two venesections during the period of the medical investigation.

The postoperative course was quite smooth. The catheter drains were removed on the fifth day. The patient was allowed up on the sixth day and was dismissed from the hospital on the twelfth postoperative day and from the clinic on the seventeenth day.

Pathologic Data.—The pathologic specimen consisted of the right middle lobe with a long hilar region where the cut ends of three vessels and two bronchi could be identified. The lobe could be roughly divided into two portions, a medial half, which could be inflated and which

appeared normal, and a lateral half, which could not be inflated but consisted of a mass of twisted varicose vessels. Intercommunications were frequent and injection with radiopaque paraffin was carried out. Long, looped, and blind-ended vascular sinuses up to 1 cm. in diameter were demonstrated, but any efforts to demonstrate discrete intercommunications between artery and vein were unsuccessful. With only a lobe to investigate, it was not possible to ascertain which

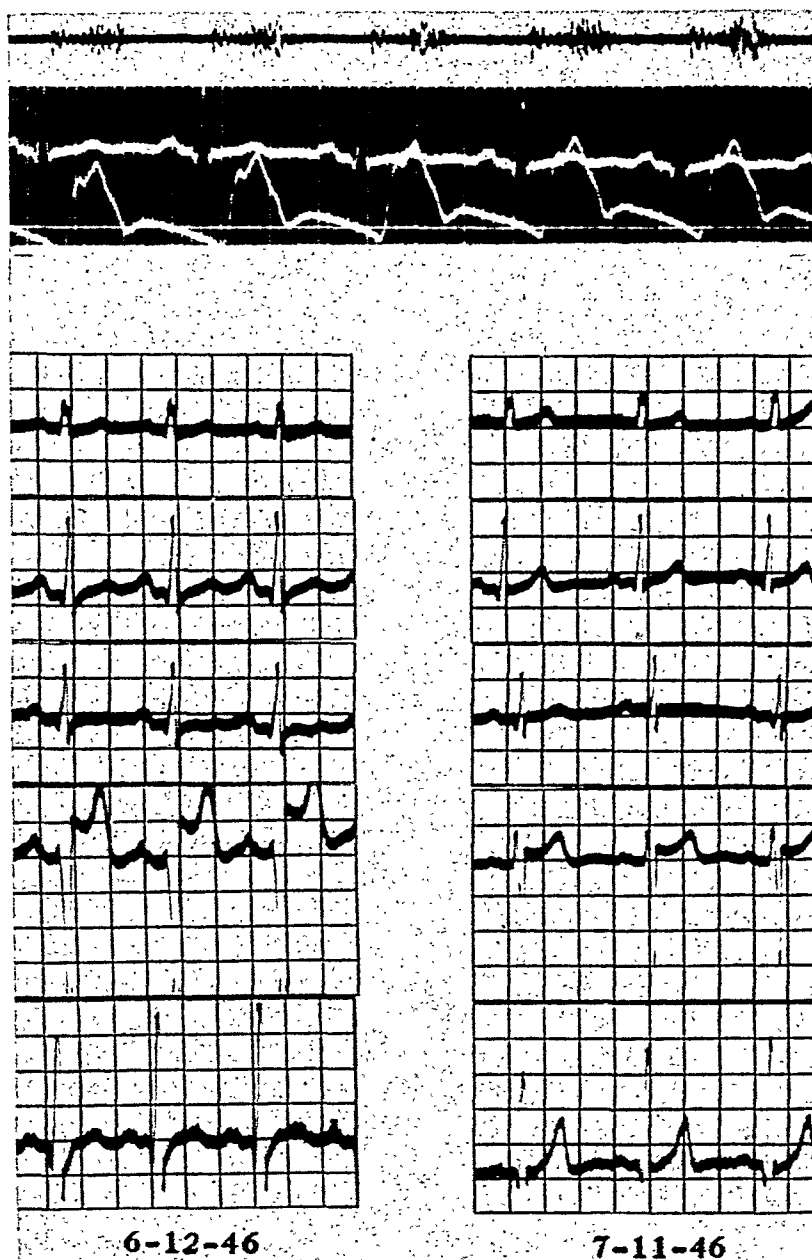


Fig. 1.—The phonocardiographic tracing in the upper figure shows the graphic representation of the late systolic bruit recorded with the microphone placed below the right nipple. The carotid pulse is shown below; Lead II of the electrocardiogram, in the middle. Phonocardiograms taken over the precordium showed normal heart sounds only. Electrocardiograms with precordial leads CR_2 and CR_3 taken preoperatively and sixteen days after operation are shown below. In the semidirect right ventricular lead there is an increase in the height of the R wave and a marked decrease in the segment elevation after operation, while in CR_3 there is practical disappearance of the S wave and increase in height of the T wave. Ten weeks after operation the electrocardiographic tracings were similar to those made sixteen days after operation.

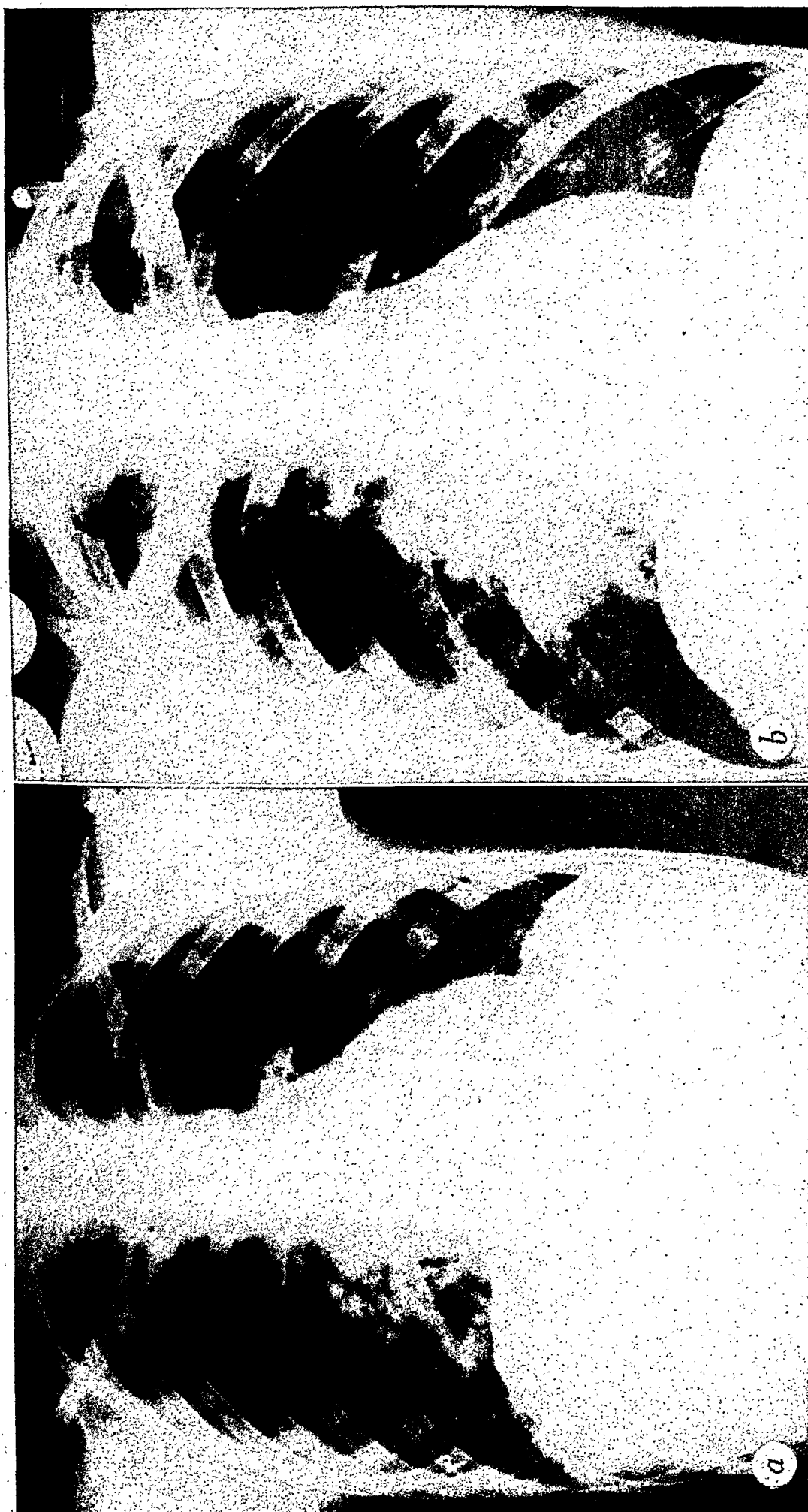


Fig. 2.—Roentgenograms in a case of pulmonary arteriovenous fistula. *a*, Taken eight years previously when patient was 12 years of age. *b*, Taken preoperatively. The lesion appears more dense in *b* than in *a*. The lobulated character of the lesion is particularly important.

blood vessel at the hilus was artery and which was vein. While some vessels over the surface of the lung were tied off previous to injection, none of the huge vessels in the pulmonary lesion appeared to communicate directly with the thoracic wall.

Histologic examination did not reveal neoplastic tissue and the blood vessels and sinuses all had elastic tissue and some muscle in their walls. That the blood sinuses had acquired arterial characters throughout the years is somewhat speculative; yet the histologic appearance was similar to that of a vein subjected to high luminal pressure over a considerable length of time. The vacuolization of the media, fragmentation of the internal elastic lamina, and some irregular intimal proliferation with muscle appearing in the intima through clefts of the elastic membrane are characteristic of thickened veins.

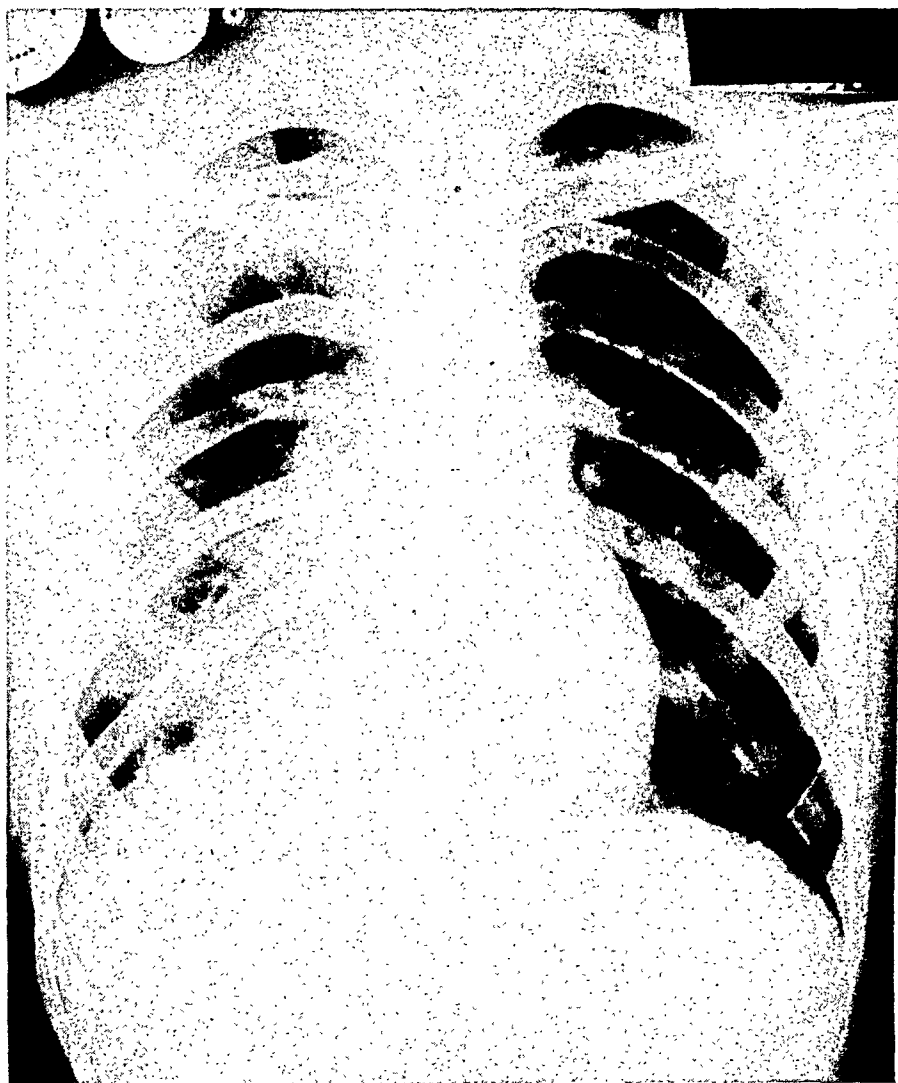


Fig. 3.—Roentgenogram in a case of pulmonary arteriovenous fistula taken ten weeks after operation. The diaphragm in the preoperative (Fig. 2, *b*) and postoperative roentgenograms is at the same height. While the right border of the heart is difficult to identify in each instance, it seems apparent that the size of the heart has decreased. The frontal cardiac area as determined by tracings on graph paper was 84 sq. cm. preoperatively and 68 sq. cm. postoperatively, which would appear significant and greater than the change that could be attributed to different phases of the cardiac cycle or to a different position of the heart.

TABLE II. LABORATORY DATA IN A CASE OF PULMONARY ARTERIOVENOUS FISTULA

	PREOPERATIVE	FIFTEEN DAYS AFTER OPERATION	TEN WEEKS AFTER OPERATION
Hemoglobin (Gm.*)	24.1	11.9	14.8
Erythrocytes (per c. mm. blood)	7,590,000	4,060,000	5,180,000
Hematocrit (per cent)	82	44	48
Blood volume (c.c. per kg.)	172	115	87
Plasma	37	64	45
Erythrocytes	135	51	42
Oxygen capacity (c.c.)	30.8	14.8	20.2
Oxygen content (c.c.)	22.8	13.7	19.0
Hemoglobin saturation (per cent)	74	93	94.1
Plasma protein (Gm. per 100 c.c. serum)	8.9	6.5	7.3
Albumin/globulin ratio	2.2/1	1.4/1	
Sodium (meq. per liter serum)	145	137.5	132
Potassium (meq. per liter serum)	4.8	4.3	4.1
Calcium (meq. per liter serum)	5.8	4.7	4.9
Carbon dioxide combining power (Vol. per 100 c.c. plasma)	48.6	60.6	65.2
Uric acid (Mg. per 100 c.c. of blood)	3.9		4.2
Basal metabolic rate (per cent)	-13		-13
Vital capacity (liters)	3.82		3.10
Venous pressure (Cm.)	11		11
Circulation times (sec.)			
Decholin	20		12
Ether	10		8

*Photometric determinations.

COMMENT

The specimens of blood taken at the time of the operation were without value in determining the volume shunt through the fistula, for the blood from the radial artery was 100 per cent saturated both before and after the hilar vessels were tied. This finding might be explained by two possibilities: either the shunt was functionally closed or the volume flow through it of venous blood of relatively high oxyhemoglobin content was sufficiently small so that this blood could be later oxygenated by the oxygen in solution in the blood. The actual oxygen tension in the lungs is unknown because of the unknown ether tension. The patient was under nitrous oxide ether anesthesia, 5 to 10 mm. of mercury positive pressure, and the alveolar oxygen tension would be approximately 550 mm. less the tension of the ether vapor. It is possible that the fistula might have closed

as a result of the operative pneumothorax. While this explanation would fit the observation that the bruit had disappeared during expiration in the original examination, it is not in accord with the operative finding of a thrill over the varicose vessels. An alternative explanation to a closure of the fistula is that the varicose vessels were draining through collateral veins to the thoracic wall and to the right side of the heart. The operative blood specimen taken from the large pulsating vessel entering the middle lobe, believed to be pulmonary artery, showed a hemoglobin saturation of 92.5 per cent. That this represents the hemoglobin saturation of mixed venous blood seems doubtful, but with such high hemoglobin content of the blood and high alveolar oxygen tension in the alveoli, it might be possible, the cardiac output being in the range of 10 to 12 liters per minute. It is possible that the high saturation of the sample could occur from reflux from a pulmonary vein, or a bronchial artery, or an intercostal artery communication. In view of the definite enlargement of the internal mammary artery, the last possibility is considered a most likely cause of the probable arterialization of the sample.

Whether the congenital vascular abnormality was originally confined to the lung proper is impossible to state; our opinion, based on the findings of other cases, is that it was. The thoracic wall attachment is believed to be a secondarily acquired condition, perhaps occurring at the time of the patient's pleurisy five years previously.

The term used for the other cases that have been reported has been either cavernous hemangioma or simply arteriovenous fistula. Any term should take into account the following factors: the congenital nature and multiplicity of the lesions; the large dilated-appearing vascular sinuses being part of the congenital defect and not entirely the result of secondary dilatation; and the frequent association of the lesion with other small vascular nevi of the skin and mucous membranes. While the term congenital arteriovenous angioma seems permissible, the preferred term to us is congenital arteriovenous varix.

The general physique of our patient resembled that of the patient in at least one of the other reported cases, but it seems doubtful whether the tall stature with long limbs could be a result of the pulmonary lesion. The ratio of his sitting height ($38\frac{1}{4}$ inches, or 97 centimeters) to his standing height ($74\frac{1}{2}$ inches, or 189 centimeters) is not abnormal for university students.¹⁷

It may be noted that the carbon dioxide combining power, or alkali reserve, was of a low normal value before operation, a fact which is in accord with primary loss of carbon dioxide under conditions of hypoxemia. This has been pointed out by Adams and associates⁸ as occurring in their patient associated with a low serum sodium. In contrast to their observation of apparent loss of base, our patient did not show evidence of loss of sodium. In fact, if serum magnesium levels were normal, he had a high normal value for the total base of the serum or serum water. Following restoration of a normal circulatory system, the values for the carbon dioxide combining power and serum cations changed to more average values. Since the basal metabolic rates were determined by collection of expired air, it was possible to re-examine the basic data for ventilation rates. Previous to operation the respiratory minute volume (expired air, saturated

20° C.) was 6.17 liters per minute with a respiratory quotient of 0.73, and after operation it was 5.48 liters per minute with a respiratory quotient of 7.3. The basal oxygen consumption preoperatively was 246 c.c. per minute; ten weeks postoperatively it was 243 c.c. per minute, and it is believed that the difference in respiratory minute volume is significant and consistent with the change in carbonate of the plasma. One thus has evidence of the same type of respiratory compensation to a lowered arterial oxygen tension of intrinsic causation as occurs with diminished oxygen tension in the environment of high altitudes.

FOLLOW-UP STUDY

At the time of his dismissal from the clinic, seventeen days after operation, the patient was feeling well, his color was normal, no bruit was present over the thorax, and he was judged to be cured. The stasis dermatitis had practically healed. The hemoglobin saturation was 93 per cent. The blood volume had not yet returned to normal and there was a relative and absolute increase in the plasma volume, perhaps a compensatory mechanism to fill the large vascular bed.

He returned to the clinic for reinvestigation on September 16, approximately ten weeks after operation, at which time he was feeling well and without complaints. His fingers and toes were little changed in shape, but there was a deep transverse groove near the base of the nails. He had not indulged in any strenuous activity and had not noticed any change in his exercise tolerance. The dermatitis of the ankles had completely healed, leaving a soft skin, normal in appearance, except for a mild degree of pigmentation. While the cardiac size, determined roentgenologically, had been well within normal limits previous to operation, there was some decrease in the roentgenographic shadow ten weeks after operation (Fig. 3). The laboratory findings were normal (Table II). There had been a slight decrease in the vital capacity, which is believed to be a temporary change.

SUMMARY

The clinical syndrome, consisting of cyanosis, clubbing of fingers, and polycythemia related to pulmonary arteriovenous fistula, is discussed and the importance of the diagnosis in view of the availability of surgical cure is emphasized.

The first case with the unusual complication of collateral circulation to the thoracic wall and with surgical cure by lobectomy is presented. It is believed that this is the ninth case of pulmonary arteriovenous fistula to be recognized clinically and reported and the fifth patient to be cured by surgical treatment.

REFERENCES

1. Hepburn, J., and Dauphinee, J. A.: Successful Removal of Hemangioma of the Lung Followed by the Disappearance of Polycythemia, *Am. J. M. Sc.* 204:681, 1942.
2. Smith, H. L., and Horton, B. T.: Arteriovenous Fistula of the Lung Associated With Polycythemia Vera: Report of a Case in Which the Diagnosis Was Made Clinically, *AM. HEART J.* 18:589, 1939.
3. Churton: Multiple Aneurysm of Pulmonary Artery, *Brit. M. J.* 1:1223, 1897.

4. Wilkens, G. D.: Ein Fall von multiplen Pulmonalisaneurysmen, Beitr. z. Klin. d. Tuberk. 38:1, 1917.
5. Rodes, C. B., Cavernous Hemangiomas of the Lung With Secondary Polycythemia, J.A.M.A. 110:1914, 1938.
6. Bowers, W. F.: Rupture of Visceral Hemangioma as Cause of Death; With Report of a Case of Pulmonary Hemangioma, Nebraska M. J. 21:55, 1936.
7. Jones, J. C., and Thompson, W. P.: Arteriovenous Fistula of Lung; Report of Patient Cured by Pneumonectomy, J. Thoracic Surg. 13:357, 1944.
8. Adams, W. E., Thornton, T. F., Jr., and Eichelberger, L.: Cavernous Hemangioma of the Lung (Arteriovenous Fistula); Report of Case With Successful Treatment by Pneumonectomy, Arch. Surg. 49:51, 1944.
9. Janes, R. M.: Multiple Cavernous Hemangiomas of the Lungs Successfully Treated by Local Resection of the Tumors, Brit. J. Surg. 31:270, 1944.
10. Goldman, A.: Cavernous Hemangioma of Lung; Secondary Polycythemia, Dis. of Chest. 9:479, 1943.
11. Mak'er, P. T., and Zion, D.: Multiple Pulmonary Hemangiomas, Am. J. M. Sc. 211:261, 1946.
12. Sisson, J. H., Murphy, G. E., and Newman, E. V.: Multiple Congenital Arteriovenous Aneurysms in the Pulmonary Circulation, Bull. Johns Hopkins Hosp. 76:93, 1945.
13. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation. Part I. Arch. Int. Med. 56:211; Part II. 457; Part III. 724; Part IV. 976; Part V. 1189, 1935.
14. D'Aunoy, R., and van Haam, E.: Aneurysm of the Pulmonary Artery With Patent Ductus Arteriosus (Botallo's Duct). Report of Two Cases and Review of the Literature, J. Path. & Bact. 38:39, 1934.
15. Boyd, L. J., and McGavack, T. H.: Aneurysm of the Pulmonary Artery; a Review of the Literature and Report of Two New Cases, AM. HEART J. 18:562, 1939.
16. Grollman, A.: The Cardiac Output of Man in Health and Disease, Charles C Thomas, 1932, Springfield, Ill., p. 325.
17. Harris, J. A., Jackson, C. M., Paterson, D. G., and Scammon, R. E.: The Measurement of Man, Minneapolis, 1930, The University of Minnesota Press, p. 215.

THE EFFECT OF CYANIDE ON THE ELECTRO-CARDIOGRAM OF MAN

CAPTAIN JACK WEXLER, CAPTAIN JAMES L. WHITTENBERGER, AND
CAPTAIN PAUL R. DUMKE

MEDICAL CORPS, ARMY OF THE UNITED STATES

STUDIES on the effect of cyanide on the electrocardiogram of man were undertaken, at first, in conjunction with experiments on therapy of cyanide poisoning. The preliminary observations on the effect of small doses of sodium cyanide were of sufficient interest to warrant an extension of the study. Although clinical observations, described in case reports by Lambert¹ and Williams,² indicated involvement of the cardiovascular system in serious or fatal cyanide poisoning, electrocardiographic tracings were not recorded.

The effect on the electrocardiogram of man given intravenous doses of sodium cyanide just sufficient to stimulate respiration was studied in sixteen normal soldiers. A dose of 0.11 mg. of sodium cyanide per kilogram of body weight, which is generally given intravenously in determining arm-to-carotid body circulation time, frequently failed to stimulate respiration. Therefore, it was necessary to inject 0.15 mg. and, in some instances, 0.2 mg. of sodium cyanide per kilogram of body weight to elicit respiratory stimulation.

The effect of lethal doses of cyanide was studied by recording continuous electrocardiographic tracings on four men executed by the inhalation of hydrocyanic acid.

RESULTS

The electrocardiograms of fifteen of the sixteen men who received 0.11 to 0.2 mg. of sodium cyanide per kilogram of body weight revealed a sinus pause, without evidence of auricular activity, which persisted for 0.88 to 4.2 seconds. In some instances nodal escape occurred before auricular activity was re-established. This sinus pause immediately preceded or accompanied the respiratory stimulation. Immediately after the pause, there were marked sinus irregularity and a slowing of heart rate for periods ranging from a few seconds to as long as two minutes which, in turn, were followed by a gradual acceleration to rates above the control levels. Control heart rate and rhythm were generally restored within three minutes. Figs. 1 to 4 illustrate these changes. The sixteenth subject failed to show a sinus pause and exhibited only a slight acceleration in heart rate at the time of respiratory stimulation.

From the Clinical Research Section of Medical Division, Chemical Warfare Service.
Received for publication Oct. 19, 1946.

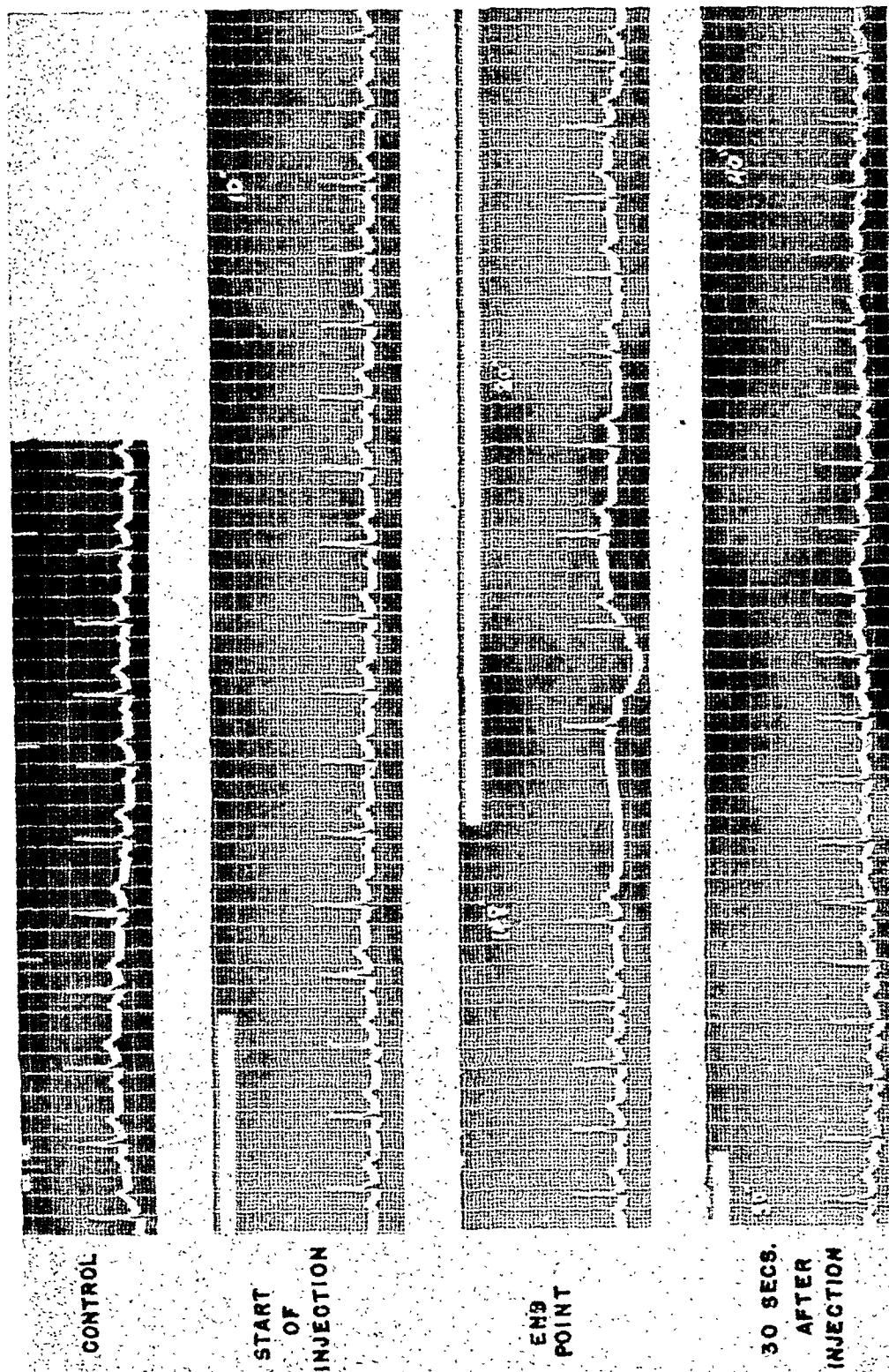


Fig. 1.—Subject B. L. Given 0.15 mg. sodium cyanide per kilogram of body weight. End point at 14.8 seconds. Sinus pause for 2.8 seconds. Nodal escape at 1.92 seconds. Ventricular complexes have been retouched in this and most of the subsequent figures.

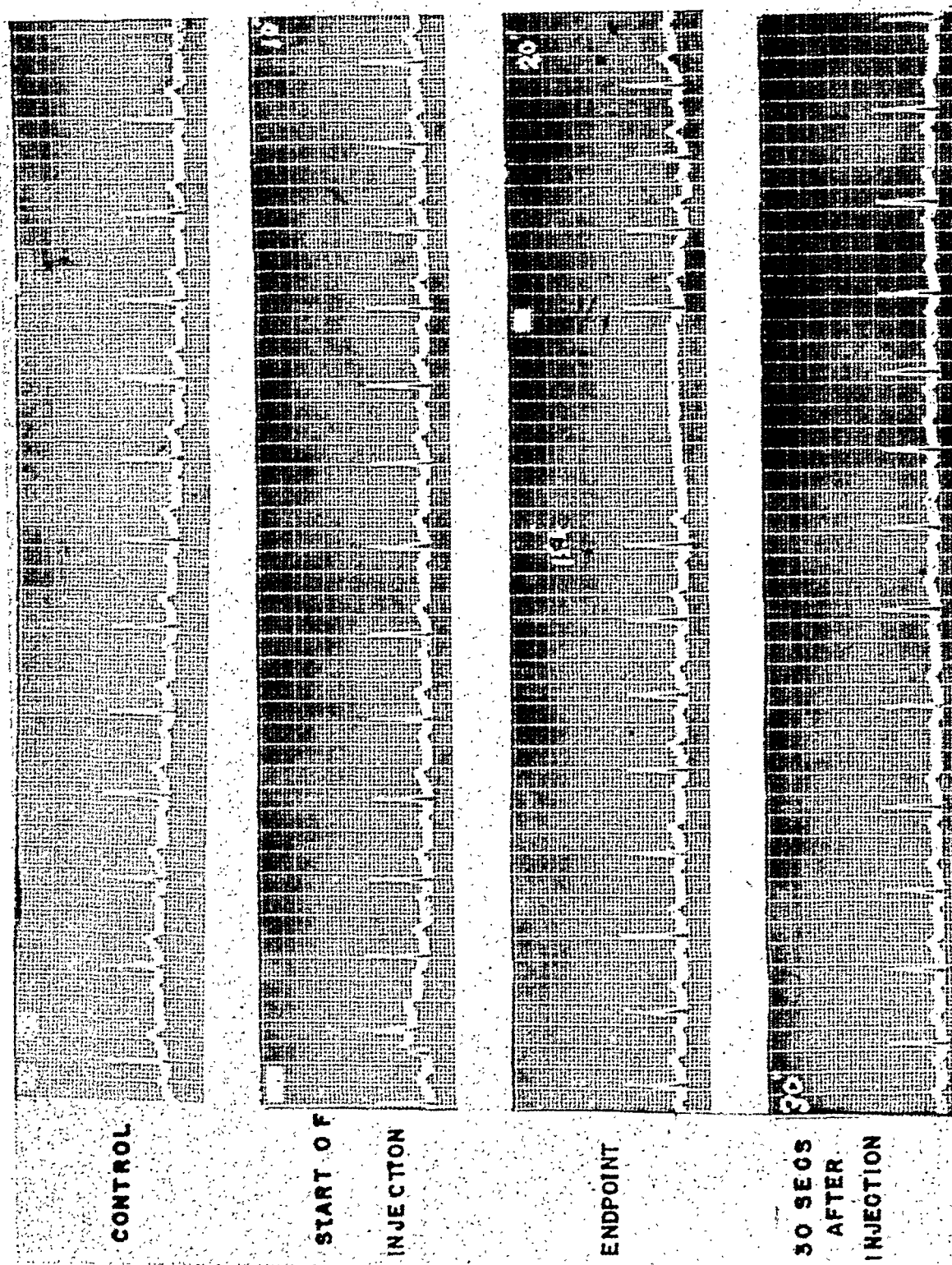


Fig. 2.—Subject G. U. Given 0.15 mg. sodium cyanide per kilogram of body weight. End point at 15.4 seconds. Sinus pause for 2.2 seconds.

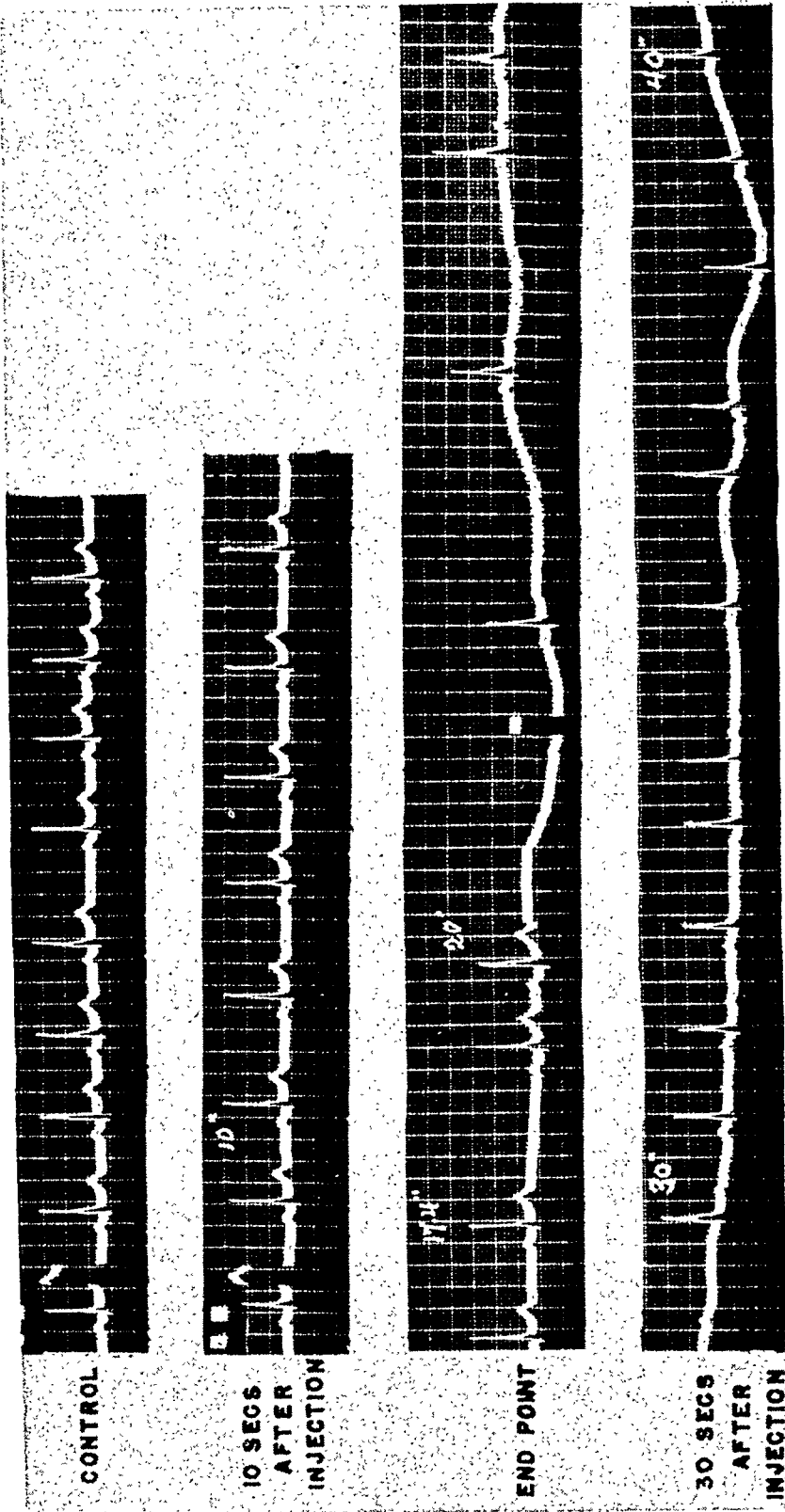


Fig. 3.—Subject O. N. Given 0.2 mg. sodium cyanide per kilogram of body weight. End point at 17.4 seconds. Marked sinus slowing and irregularity for approximately one minute.

The four men executed by inhalation of hydrocyanic acid exhibited striking electrocardiographic aberrations. The records of three of the four subjects are shown in Figs. 5A, 5B, 6A, 6B, 6C, 7A, and 7B.

"Control" records obtained after the men were strapped in the execution chair, but before the hydrocyanic acid was generated, revealed initial heart rates varying between 102 and 166 beats per minute.

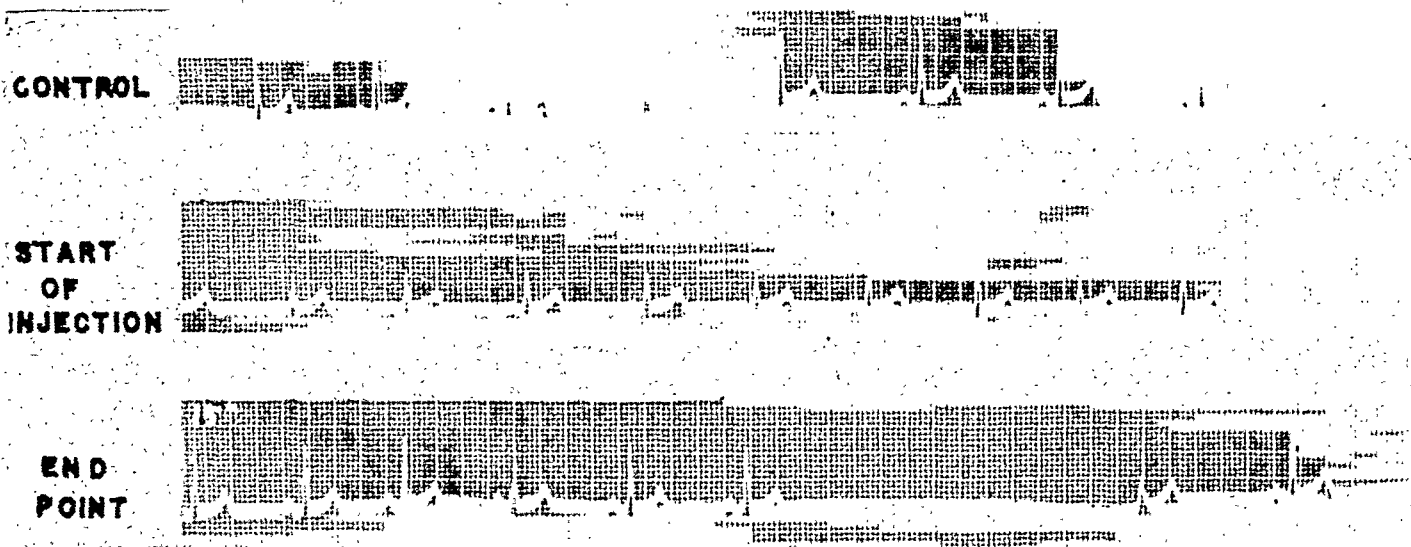


Fig. 4.—Subject M. O. Given 0.2 mg. sodium cyanide per kilogram of body weight. End point at 19.2 seconds. Sinus pause for 4.2 seconds. Nodal escape at 3.2 seconds. (Control and end point in Lead II; start of injection in Lead I.)

All four subjects revealed a marked slowing of heart rate which reached its nadir between the first and third minutes. This slowing was accompanied by sinus irregularity and eventually by complete disappearance of P waves. During the period of auricular arrest, the rhythm was auriculoventricular nodal in two and idioventricular in the other two subjects. A secondary increase in rate, but not to "control" levels, was observed during the third and fourth minutes along with the irregular reappearance of P waves, some of which were not conducted. All subjects showed A-V dissociation with a secondary decrease in rate during the fifth minute (Fig. 6B). During the sixth and seventh minutes, the heart rate again showed a slight increase and a return to normal sinus rhythm.

Thereafter, the heart rate slowed progressively. Normal A-V conduction in one man and A-V conduction with incomplete A-V block in a second were maintained throughout the period of observation (approximately thirteen minutes). A third subject developed Wenckebach's phenomenon, 2:1 block, and, finally, complete heart block. The fourth subject maintained normal A-V conduction until the fourteenth minute, when he developed ventricular tachycardia and ventricular fibrillation (Fig. 7B).

The QRS complexes exhibited marked changes in voltage and form. Since these changes were accompanied by changes in rhythm and rate, and by changes in position of the subjects, incident to slumping and twisting, their significance is obscure. One subject exhibited transitory right axis deviation (Fig. 5A). Intraventricular conduction time was normal except in two subjects during periods of idioventricular rhythm (Fig. 6A).

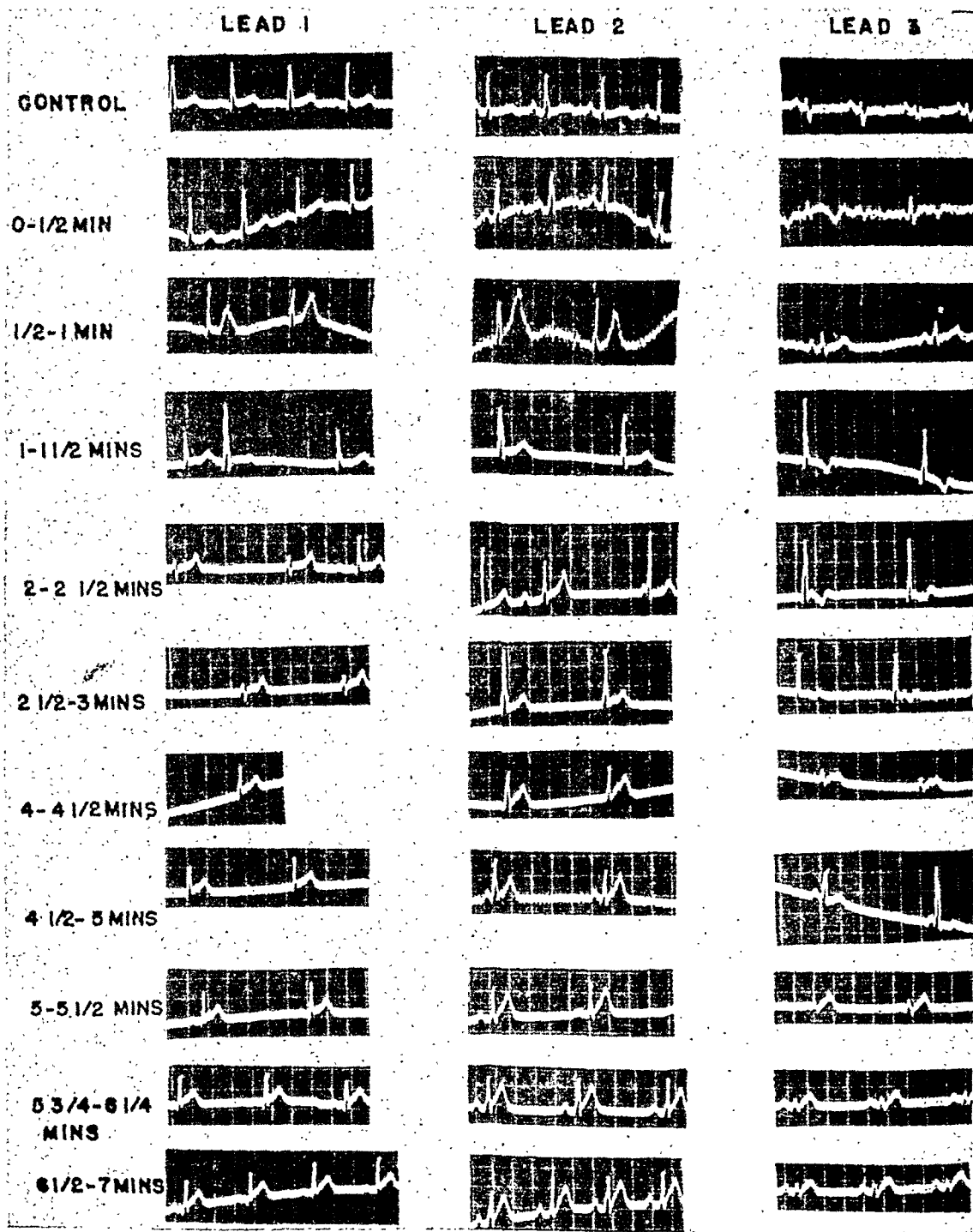


Fig. 5A.—Subject X. 0 time indicates start of execution.

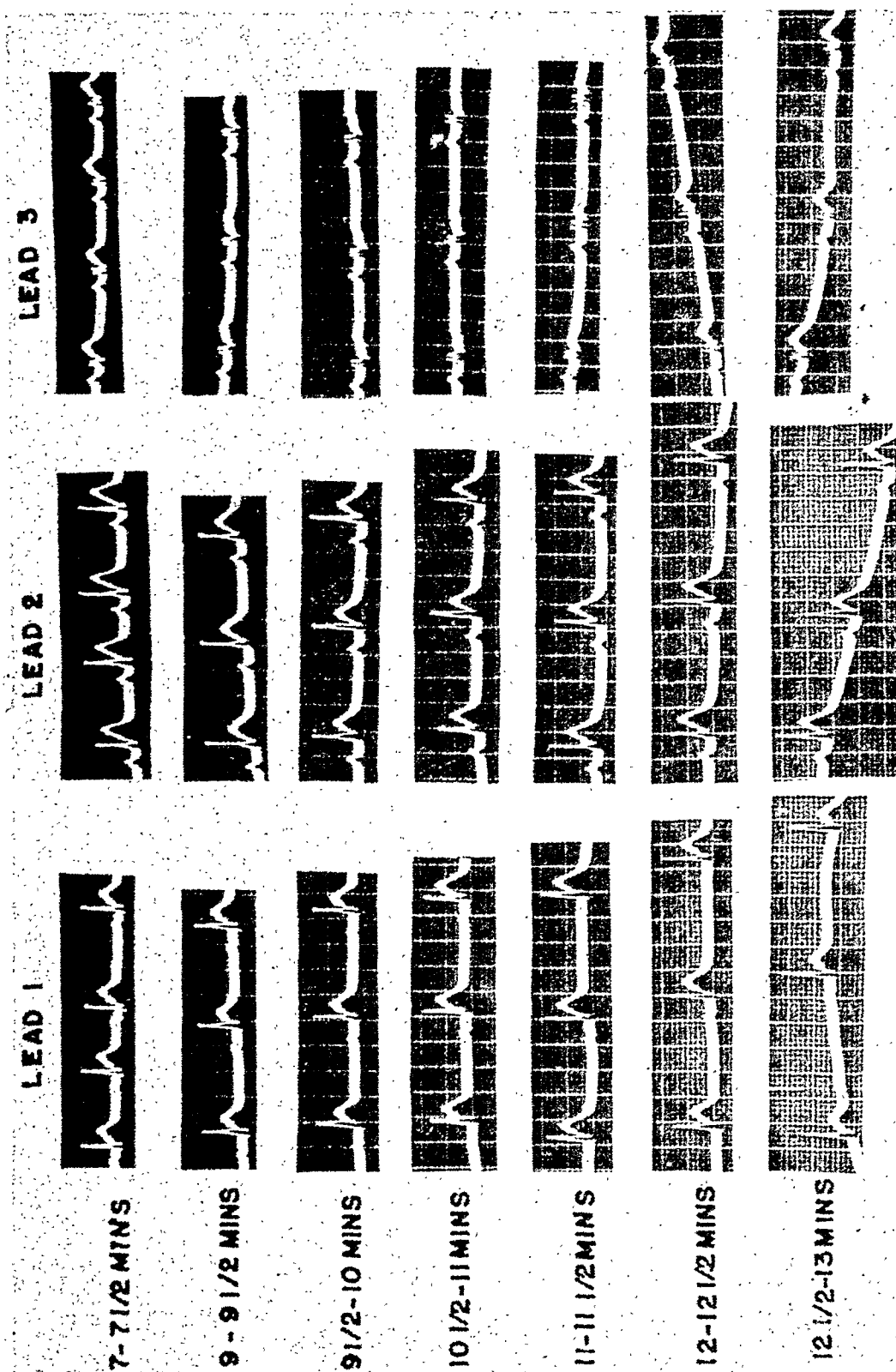


Fig. 5B.—Subject X. Recording was discontinued at thirteen minutes.

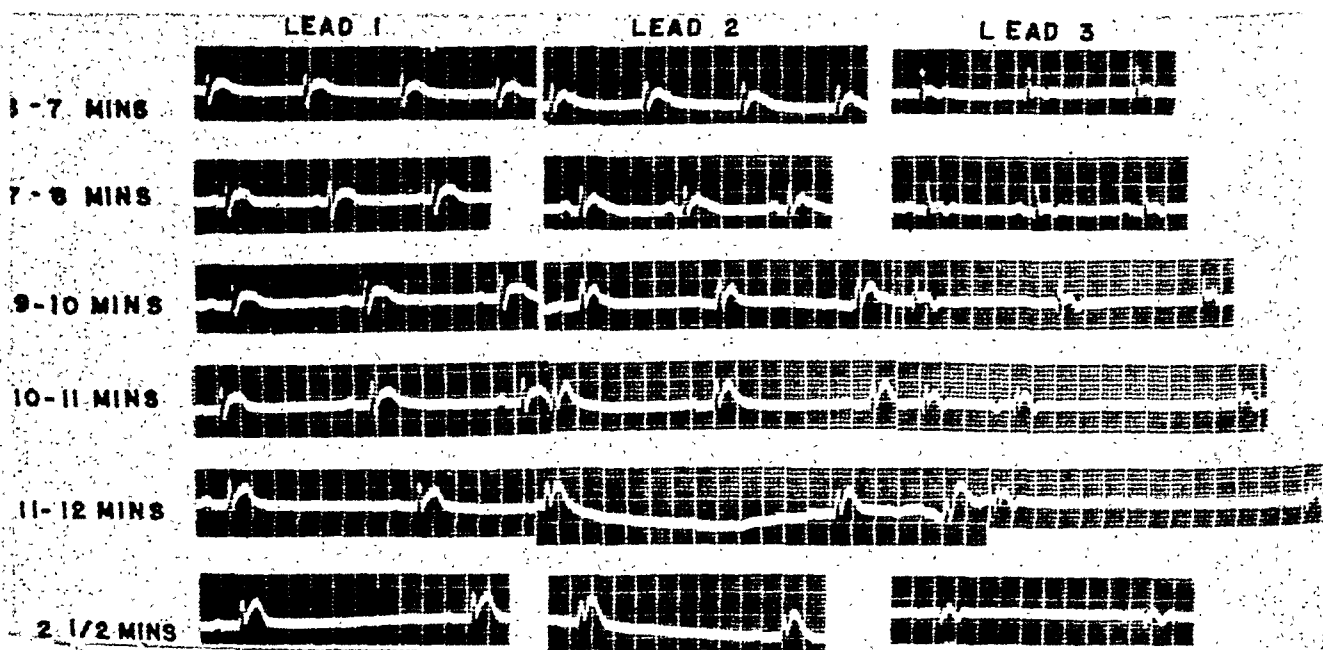
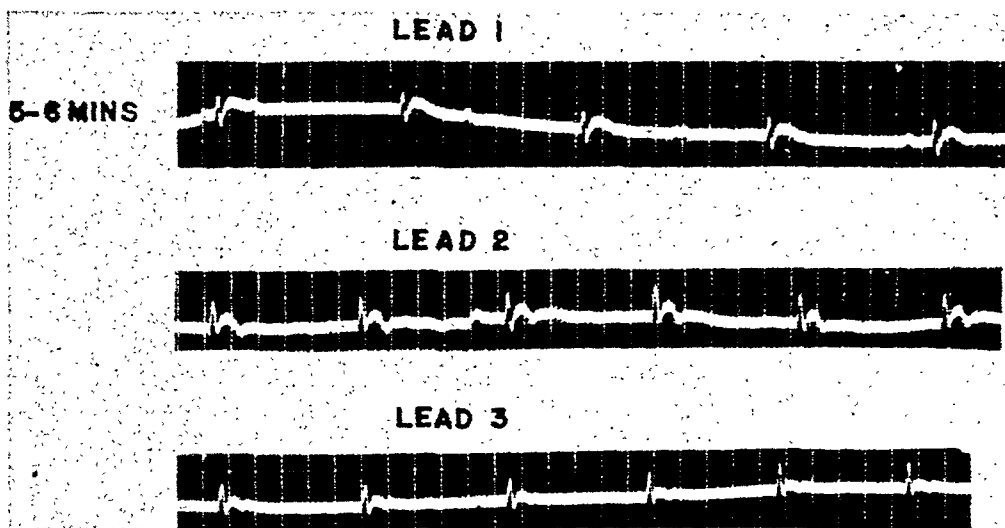
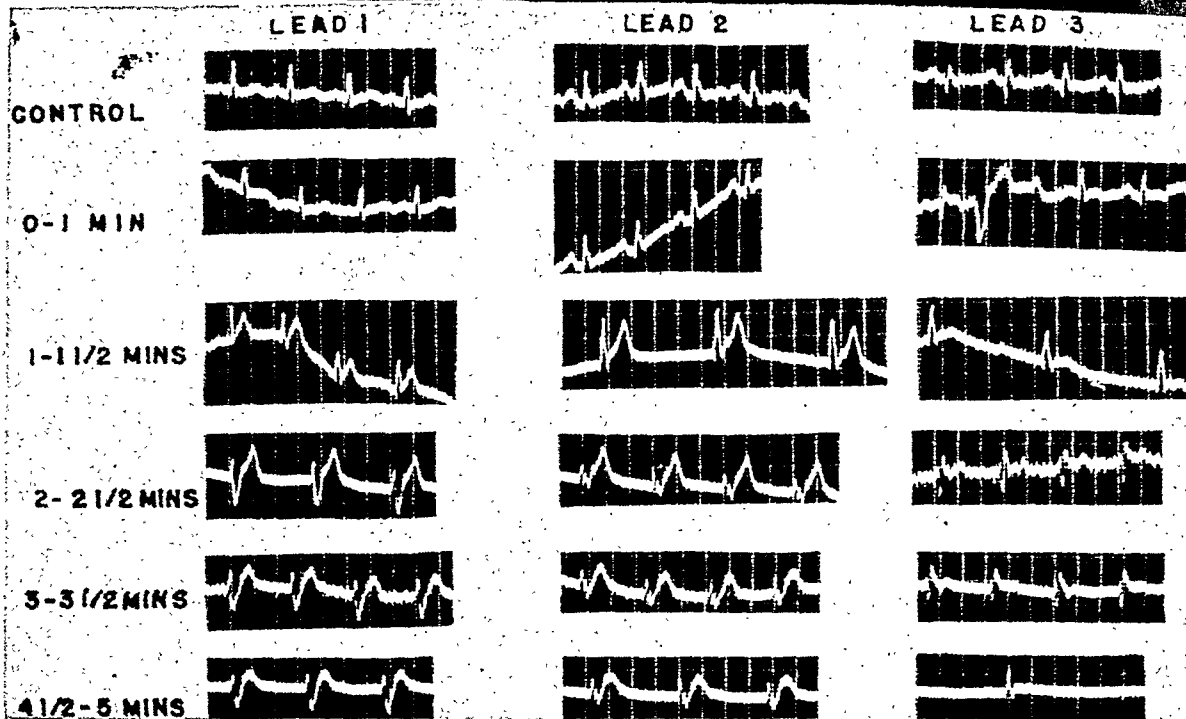


Fig. 6.—Subject Y. 0 time indicates start of execution. Asystole for five seconds.

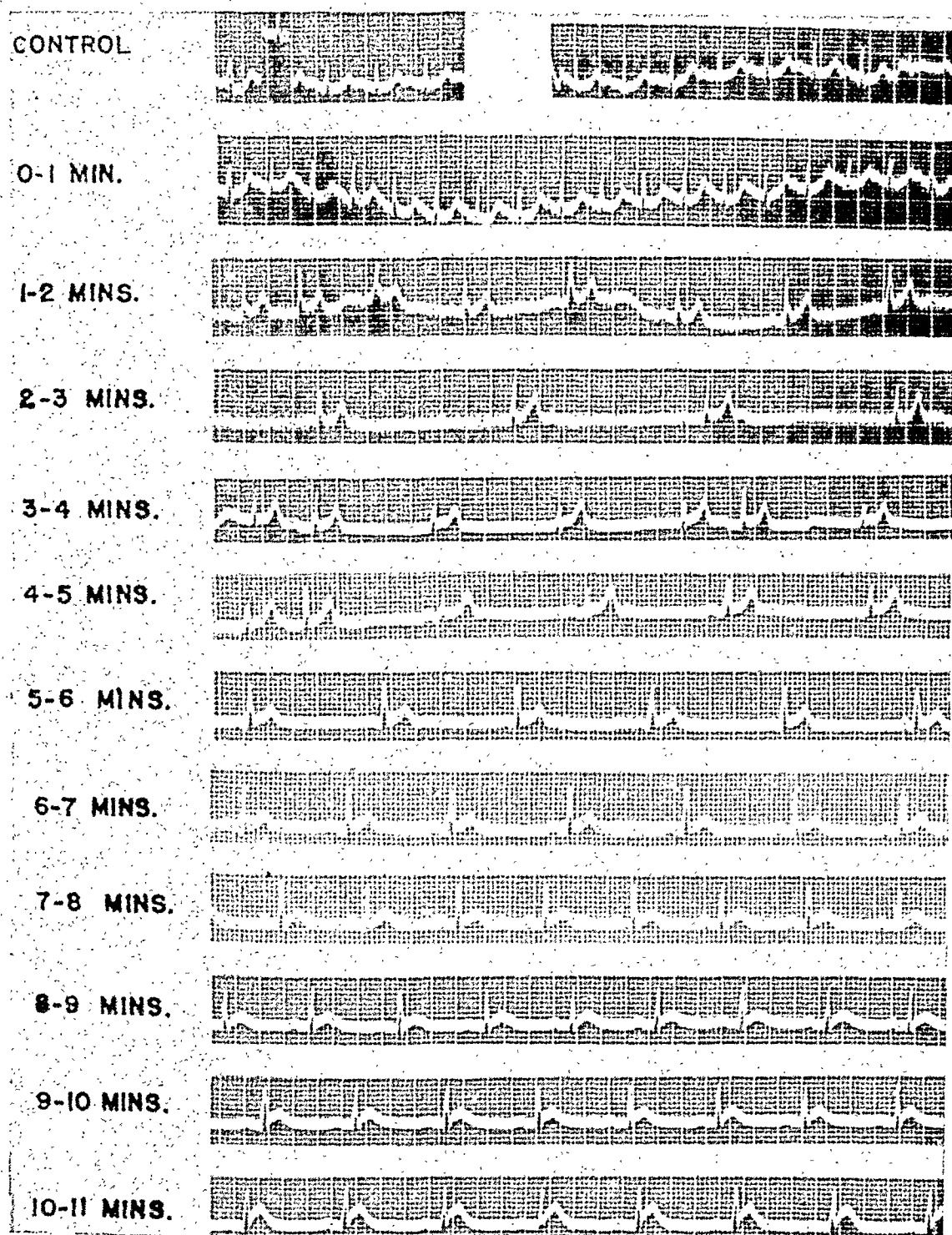


Fig. 7A.—Subject Z. All tracings recorded in Lead I.

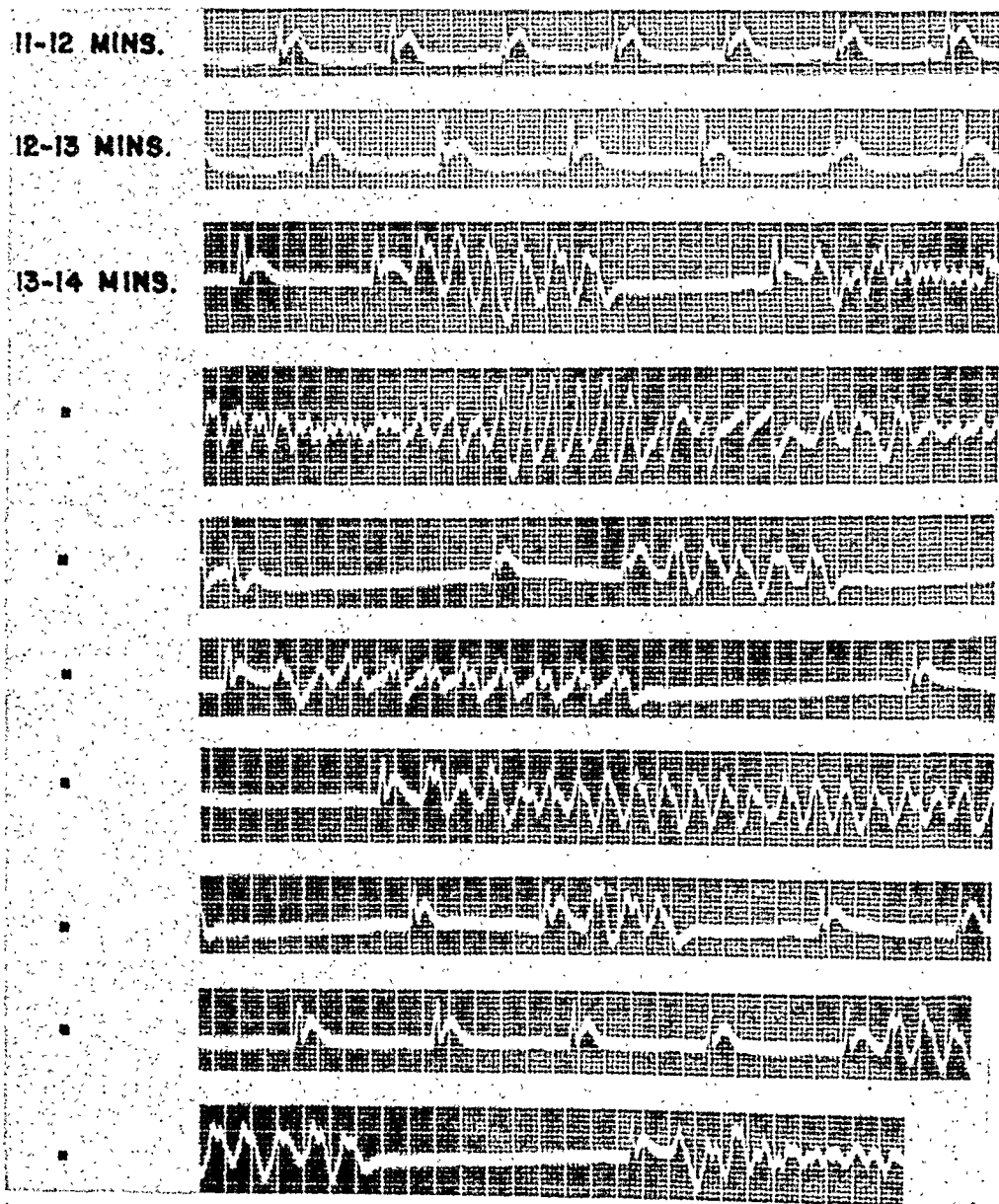


Fig. 7B.—Subject Z. All tracings recorded in Lead I.

T waves showed an early but transient increase in amplitude (most marked in the subject whose tracings are shown in Fig. 5A). There was progressive shortening to the point of disappearance of the S-T segments. Terminally the T waves originated high on the R wave.

DISCUSSION

The mechanisms responsible for the changes which have been described are complex. The following factors play a role:

1. Reflex stimulation of the cardioinhibitory, cardioaccelerator, and vasomotor centers via the carotid and aortic bodies.
2. The central action of cyanide on the cardiac and vasomotor centers.
3. The direct toxic effect of cyanide on the heart.
4. The additive effect of anoxia due to respiratory arrest.

In dogs, the early changes in rhythm and rate which are similar to those observed in man³ can be diminished by atropine or abolished by bilateral vagotomy and denervation of the carotid body. Thus, the early changes are neurogenic and are due to reflex or central effects of cyanide, whereas the late changes are due to the direct toxic action of cyanide on the heart plus the effect of anoxia.

The electrocardiographic changes observed with small doses of sodium cyanide (periods of asystole varying from 0.88 to 4.2 seconds) offer a possible explanation for the untoward and, at times, alarming reactions which have occasionally been observed when sodium cyanide is injected intravenously for determination of arm-to-carotid body circulation time. It is possible that in the presence of organic heart disease alterations in rhythm and rate resulting from a small dose (0.11 mg. per kilogram of body weight) of sodium cyanide may be even more striking than those observed in our normal subjects. One of our subjects (Fig. 4) had momentary dim-out during the test.

SUMMARY

1. The electrocardiographic changes resulting from intravenous injection of small doses of sodium cyanide and from inhalation of lethal doses of hydrocyanic acid are described.
2. The mechanisms by which these effects are produced are discussed.
3. The period of asystole which results from small doses of sodium cyanide (0.11 to 0.2 mg. per kilogram of body weight) even in normal hearts is offered as a possible explanation for the untoward and, at times, alarming reactions which have been observed when sodium cyanide is used to determine arm-to-carotid body circulation time.

REFERENCES

1. Lambert, S. W.: Poisoning by Hydrocyanic Acid Gas, With Especial Reference to Its Effect Upon the Brain, *Neurol. Bull.* 2:93, 1919.
2. Williams, C. L.: An Unusual Case of Cyanide Poisoning During Fumigation, *Pub. Health Rep.* 53:2,094, 1938.
3. Wexler, Jack: Unpublished data.

CIRCULATORY BLOOD VOLUME OF SOME ORGANS

GUSTAV NYLIN, M.D.

STOCKHOLM, SWEDEN

AS FAR as I know, no previous attempts have been made to ascertain, on living human beings during a surgical operation, the amount of circulating blood in one of the lungs or in the spleen. On the other hand, Grosse-Brockhoff and Molineus¹ and Asmussen,² by means of the carbon monoxide method, have determined the amount of circulating blood in the lower extremities. The circulation to a part of the lower limbs was occluded by the application of pneumatic cuffs around the thighs. The quantity of circulating blood in the rest of the body was then determined by both the dye method and the carbon monoxide method. After this, the cuffs were deflated and new samples of blood were taken for analysis. Asmussen found that the circulating blood volume through the lower limbs below the cuff amounted to 1 liter, or 17.3 per cent of the total circulatory blood volume. As pointed out by Asmussen, certain pronounced sources of error are inherent in both the dye method and the carbon monoxide method. The chief error in the latter method is the result of the fact that myoglobin absorbs carbon monoxide.

The method elaborated by Hevesy and his collaborators^{3,4} for labelling red blood corpuscles with radioactive phosphorus has made possible certain studies of the circulatory system which had been impossible before. When labelled blood corpuscles are injected intravenously into a normal person, mixture with the circulating blood soon takes place;⁵⁻⁷ in some instances, within less than one minute after the injection and, in almost every other instance, in less than five minutes. After mixing has been accomplished, the injected blood corpuscles maintain their activity at a constant level long after the injection, even up to one hour. This important phenomenon renders a study of experimental changes in circulatory conditions possible within one hour. Hitherto, no method offering similar advantages has been at our disposal.

METHOD

Eight cubic centimeters of blood taken from the patient by venous puncture are shaken in a water bath at a temperature of 37° C. for two hours with radioactive disodium acid phosphate containing about 0.05 millicuries of radioactive phosphorus. A small amount of heparin is added to this compound to prevent

From the Medical Clinic II of Sabbatsberg's Hospital.
Received for publication Nov. 20, 1946.

blood clotting. Half of the labelled blood is then reinjected into the patient on whom studies are to be made during operation. The other half of the blood is measured with regard to its activity on plasma as well as on corpuscles. Determination of the hematocrit values is carried out simultaneously on samples of blood from the patient. Just before injecting the tagged erythrocytes into the circulatory system, the surgeon occludes the circulatory passage to one of the lungs. After the injection of the labelled blood into the patient, who is undergoing pneumonectomy or splenectomy during anesthesia, a certain fixed time is allowed to elapse in order to obtain a mixture of the labelled blood corpuscles and the circulating blood. Several samples of blood are drawn from the patient before circulation to the occluded organ is released, four to twenty-four minutes after the injection of the labelled blood. During this comparatively long period of time required for the mixing, care must be taken to maintain a constant level of the activity of the circulating blood. After this, the circulation to the occluded organ (the lung or the spleen) is released and new blood samples are taken by venous puncture up to one hour after the injection of labelled blood. All of the samples, to which a small amount of heparin has been added, are then centrifuged and the plasma removed. Finally, the blood corpuscles are weighed, dried and pulverized, and their activity measured.

RESULTS

In the present investigation, three cases were subjected to extirpation of one lung because of bronchogenic carcinoma. In a fourth case, a normal person, the circulation to the lower limbs was occluded by pneumatic cuffs around the thighs for the purpose of studying the circulating volume of blood in the lower part of the limbs.

Determination of Circulatory Blood Volume of One Lung Before Lung Extirpation in Three Cases of Bronchogenic Carcinoma.—

CASE 1.—After thoracotomy and exploration of the left lung, the pulmonary artery to this lung was occluded. Immediately afterwards, the patient's own labelled corpuscles were injected intravenously. The surgeon then waited while all the samples of blood from a brachial vein of the patient were taken. Several samples were drawn from the fourth to the seventeenth minute after the injection of the tagged erythrocytes. Eighteen minutes after the injection the pulmonary artery to the lung concerned was released, and new specimens of blood were collected up to twenty-five minutes after injection. All the samples were measured with regard to their activity by means of the Geiger equipment. The results are illustrated in Fig. 1. From this diagram, it may be seen that the specific activity of the blood samples during the time when the left lung was cut off from circulation was remarkably constant and, furthermore, that the circulating corpuscle volume in the rest of the body amounted to 2,184 Gm., or 2,359 cubic centimeters. The total circulating blood volume was calculated to equal 5,904 c.c., with a hematocrit value of 0.40. After release of the pulmonary artery to the left lung, the specific activity decreased under the influence of dilution by the blood blocked in the lung. The circulatory blood corpuscle volume, accordingly, increased to 2,550 Gm., or 2,752 c.c., and the total circulatory blood volume to 6,882 cubic centimeters. Thus, the circulatory blood volume of the left lung amounted to 978 c.c., or 14.3 per cent of the total circulating blood volume.

CASE 2.—After thoracotomy and exploration of the left lung, the vessels leading to the same lung were occluded and tagged erythrocytes were injected intravenously. Blood samples were

then collected four and twelve minutes later. Immediately after the blood samples were obtained, the vessels were released and a new series of blood samples were taken. The values of the specific activity of the samples are recorded in Fig. 2. As in Case 1, the specific activity had become almost constant before the release of the circulation to the left lung. After the circulation had been restored, the activity decreased and attained a constant level from the sixteenth to twenty-fifth minute after the injection of the labelled corpuscles. The circulating corpuscle

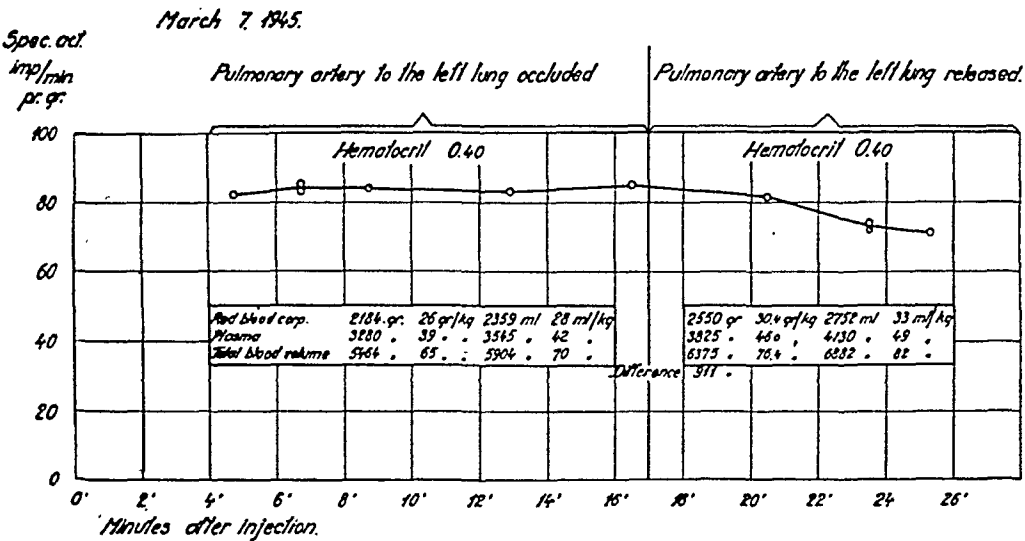


Fig. 1.—Case 1. Determination of the circulating blood volume of one lung. See text.

March 9, 1945

J 399/45

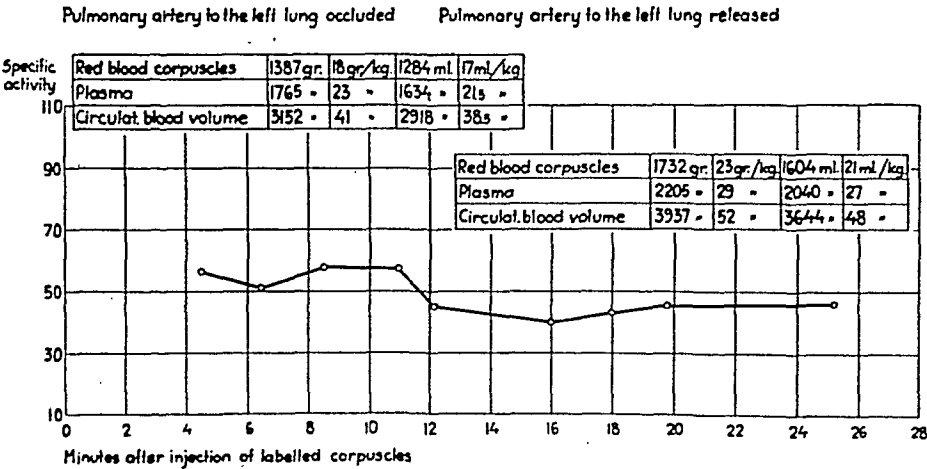


Fig. 2.—Case 2. Determination of the circulating blood volume of one lung. See text.

volume was calculated to equal 1,387 Gm., or 1,284 c.c., while the circulation to the lungs was blocked. These values were 1,732 and 1,604, respectively, when the circulation was released. During occlusion of the vessels to the left lung, the total circulatory blood volume amounted to 2,918 c.c.; when the circulation was restored, this value became 3,644 cubic centimeters. The difference was calculated to be 20 per cent. This is a rather high value for the circulatory blood volume of one lung.

CASE 3.—Right-sided pulmonectomy was undertaken because of bronchogenic carcinoma. Four hundred fifty c.c. of blood were given intravenously fifty minutes after the beginning of thoracotomy. Twenty-five minutes later, all the vessels and the main bronchus to the right lung

were occluded. The lung was then seen to be atelectatic. Twenty-nine minutes after the occlusion, the labelled blood was injected into the right pulmonary artery and blood samples were collected ten and fifteen minutes later. The vessels, but not the bronchus, were then released to the same lung. The lung, therefore, had a free circulation but still remained atelectatic. The specific activity, as shown in Fig. 3, decreased to a constant level from the twenty-second to the fortieth minute. The main bronchus to the right lung was then released and the lung expanded. At the same time the activity decreased even further.

The circulatory corpuscle volume and the total circulatory blood volume were calculated, first, during the period when both the vessels and the bronchus were clamped, and, second, after only the vessels had been released, and third, after the bronchus had also been freed. As illustrated in Fig. 3, the total circulatory blood volume during the first stage of operation when both the vessels and the bronchus were occluded amounted to 3,870 cubic centimeters. It increased to 4,100 c.c. when only the vessels were freed, and to 4,640 c.c. when the bronchus also was released. Consequently, when only the circulation to the right lung, which was partially atelectatic, was released, the circulating blood volume to that lung amounted to 4.9 per cent of the total circulatory blood volume. When the bronchus to that lung also was freed, some stored blood in the right lung must have been thrown into the circulation, since the activity continued to decrease. The calculated circulatory blood volume of the right lung then amounted to 16.6 per cent of the total circulating blood volume.

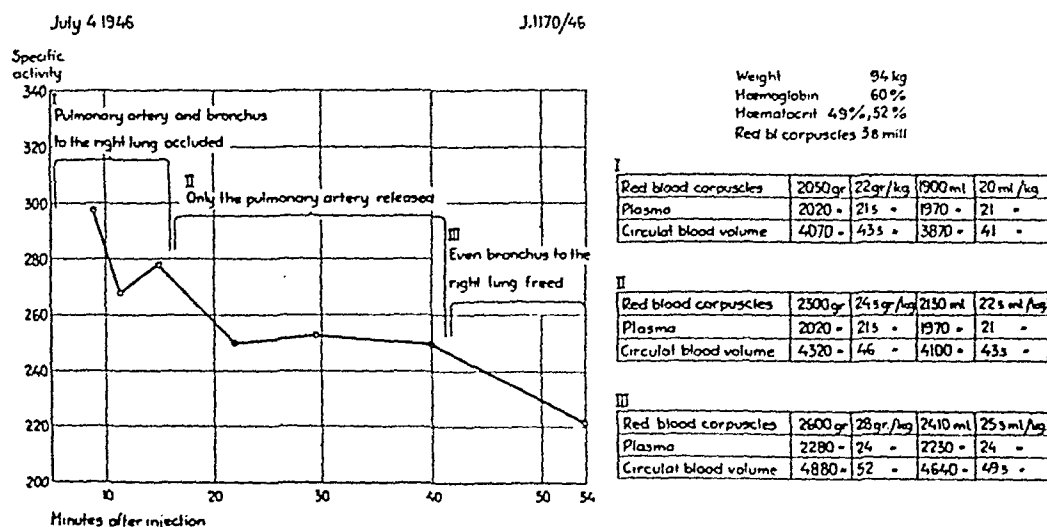


Fig. 3.—Case 3. Determination of the circulating blood volume of one lung. See text.

From these results it apparently may be concluded that blood is stored in an atelectatic lung when the ventilation is either bad or obstructed. The working of this mechanism is difficult to explain. It may be assumed that the arterio-venous anastomoses open during bad ventilation, and that the capillaries to certain parts of the lung are stored with unaerated blood.

In Case 1 the circulatory blood volume of one lung amounted to 14.3 per cent of the total circulatory blood volume, in Case 2 to 20 per cent, and in Case 3 to 16.6 per cent. The mean value of these determinations in three patients indicate that the circulatory blood volume of one lung is as much as 17 per cent of the total circulatory blood volume.

Determination of Circulatory Blood Volume of Part of Lower Limbs.—

CASE 4.—This patient, a man, was being treated for duodenal ulcer. In the morning the patient was placed in a recumbent position and blood pressure cuffs were applied to the lower limbs. The pressure in the cuffs was elevated above the blood pressure of the lower limbs for

twelve minutes. Immediately after starting the occlusion of the circulation to the lower limbs, the tagged erythrocytes were injected intravenously. Samples of blood were measured with regard to their activity at the fifth to the twelfth minute after the injection. A constant level was obtained. The circulation was then released to the legs. The result was dilution in the activity of the blood. Equilibrium was soon established and a constant level was present in the samples of blood taken from the twenty-fifth to the sixtieth minute after injection. The values of the specific activity of the samples of blood are shown in Fig. 4. The circulating blood volume was calculated during the period of occlusion of the circulation to the lower limbs and was found to be 3,805 cubic centimeters. After deflation of the cuffs, it increased to 4,405 cubic centimeters. The calculated circulatory blood volume to a part of the lower limbs amounted, therefore, to 600 c.c., or 13.6 per cent of the total circulatory blood volume.

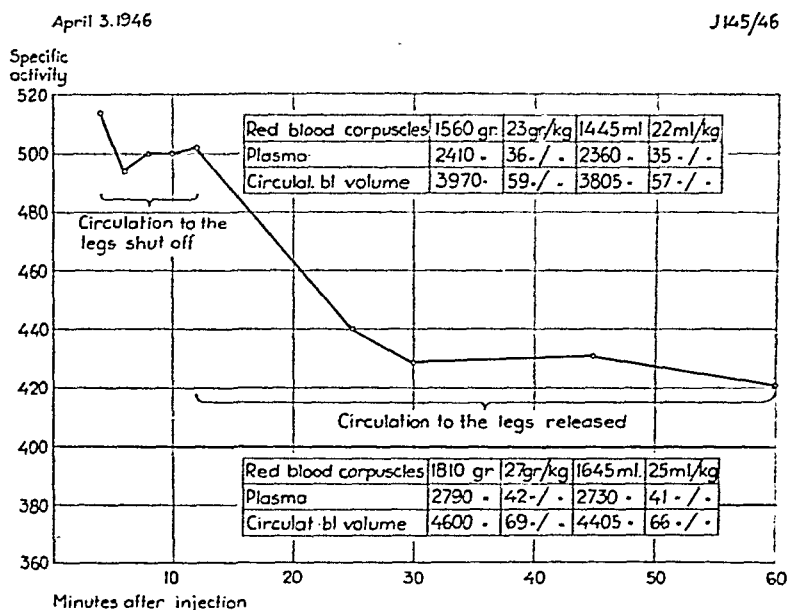


Fig. 4.—Case 4. Determination of circulating blood volume of the lower limbs. See text.

SUMMARY

1. The fact that injected tagged erythrocytes maintain a constant level of activity in the circulation up to a minimum of one hour after the injection has made it possible to study certain unsettled circulatory problems.
2. The circulatory blood volume of one lung during pulmonectomy has been determined by means of tagged erythrocytes in three patients. The mean value of the circulatory blood volume through one lung has been shown to be 17 per cent of the total circulating blood volume.
3. The circulatory blood volume of the lower limbs has been determined and found to be 13.6 per cent of the total circulating blood volume.

I am greatly indebted to Clarence Crafoord, Head Surgeon of the Surgical Chest Clinic, who has afforded me facilities for carrying out these investigations in the course of operation.

I also wish to express my sincere thanks to The Board of Swedish Medical Research for the grants bestowed in connection with this investigation.

I beg to extend my warm thanks to Professor G. de Hevesy, for his unfailing interest, and to Professor Manne Siegbahn, who kindly placed radioactive phosphorus at my disposal.

REFERENCES

1. Grosse-Brockhoff, F., and Molineus, W.: Untersuchungen über die Blutdepots des Menschen, *Deutsches Arch. f. klin. Med.* 185:481, 1940.
2. Asmussen, E.: On Determination of Blood Volume by CO-method, *Acta physiol. Scandinav.* 3:156, 1942.
3. Hevesy, G., and Hahn, L.: Method of Blood Volume Determination, *Acta physiol. Scandinav.* 1:3, 1940.
4. Hevesy, G., and Zerahn, K.: Determination of the Blood Corpuscle Content, *Acta physiol. Scandinav.* 4:376, 1942.
5. Nylin, G., and Malm, M.: Concentration of Red Blood Corpuscles Containing Labeled Phosphorus Compounds in Arterial Blood After Intravenous Injection; Preliminary Report, *Am. J. M. Sc.* 207:743, 1944.
6. Nylin, G.: Dilution Curve of Activity in Arterial Blood After Intravenous Injection of Labeled Corpuscles, *AM. HEART J.* 30:1, 1945.
7. Nylin, G.: Blood Volume Determinations With Radioactive Phosphorus, *Brit. Heart J.* 7:81, 1945.
8. Nylin, G.: *Arkiv för Kemi, Mineralogi och Geologi*; published by the Swedish Royal Academy of Science, 20A:No. 17, 1945.

INTRUSION OF AORTIC ROOT INTO MITRAL ORIFICE IN HYPERTENSIVE DISEASE; RADIOLOGIC OBSERVATIONS ON LIVING PERSONS

FRANK WINDHOLZ, M.D., AND CHARLES E. GRAYSON, M.D.
SAN FRANCISCO, CALIF.

RECENT experience^{1,2} gained in radiologic studies of calcified intracardial structures shows that not only the mitral annulus fibrosus is recognizable, but also adjacent calcified areas of the "fibrous skeleton"^{3,6} of the heart, such as the fibrous trigona (central fibrous bodies) and the aortic ring with its supporting fibers. If these structures are calcified they can be identified easily, and the position, spatial interrelationship, and movements can be studied in living persons. Using the proper technique,^{1,2} the frequency of radiologic demonstration of intracardial calcifications gradually approaches their pathoanatomic incidence. This amounts to 7 (5 to 10 per cent) in one hundred patients of all ages and to 20 per cent in those after the fifth decade.^{4,5} This estimation, however, includes also minute calcifications, the visualization of which in living persons is not practicable with the present facilities.

The configuration of the normal mitral ostium is generally considered as being ellipsoid with occasional slight flattening of the anteromedial aspect. The degree and extent of the flattening is not specified in anatomic descriptions at our disposal. The mitral annulus fibrosus does not completely encircle the mitral ostium. It is a horseshoe-shaped part of the ellipsoid, situated on the posterior, lateral, and anterior aspects of the ostium. The medial portions are not surrounded by the fibrous annulus. In this area the posterolateral section of the aortic ring and its supporting fibers, contiguous portions of the trigona, and fila coronaria^{3,6} form the mitral ring. Fig. 1 shows the anatomic appearance of the mitral orifice after the removal of the auricles. The typical roentgen appearance of the calcified mitral annulus fibrosus with no calcifications in the constituent posterolateral section of the aortic ring is illustrated in Fig. 2. The calcification is horseshoe-shaped, like the annulus itself. The ring is incomplete. With progress of calcareous deposit the aortic ring also may become involved. In such instances both structures together form a rigid, continuous calcified circle or ellipsoid around the mitral orifice, as seen in Fig. 3.

From the anatomic view of the atrioventricular ostia also can be seen the close proximity of the root of the aorta and the mitral orifice. This explains that pathologic variations in the size and shape of the aortic root might in-

From the Department of Radiology, Stanford University, School of Medicine.
Received for publication Nov. 18, 1946.

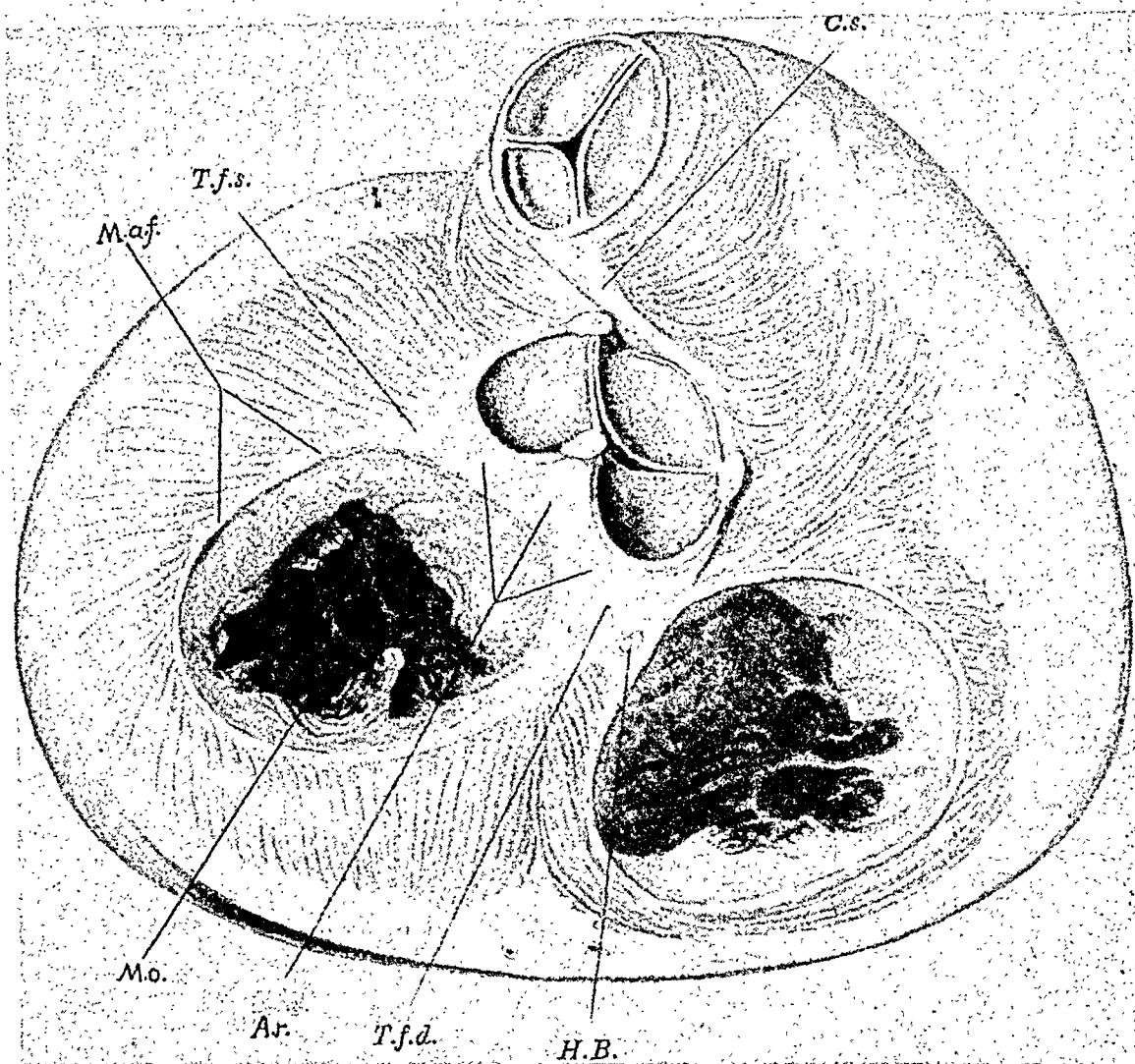


Fig. 1.—View of the fibrous skeleton of the heart and of anatomic relationship of aorta and mitral ostium after removal of the auricles. *M.o.*, mitral ostium; *M.a.f.*, mitral annulus fibrosus; *A.r.*, aortic ring; *T.f.s.*, left fibrous trigonum; *T.f.d.*, right fibrous trigonum; *C.s.*, tendon of pulmonal conus; and *H.B.*, bundle of His. (After Tandler, J.: *Anatomie des Herzens*, Jena, 1913, Gustav Fischer.)

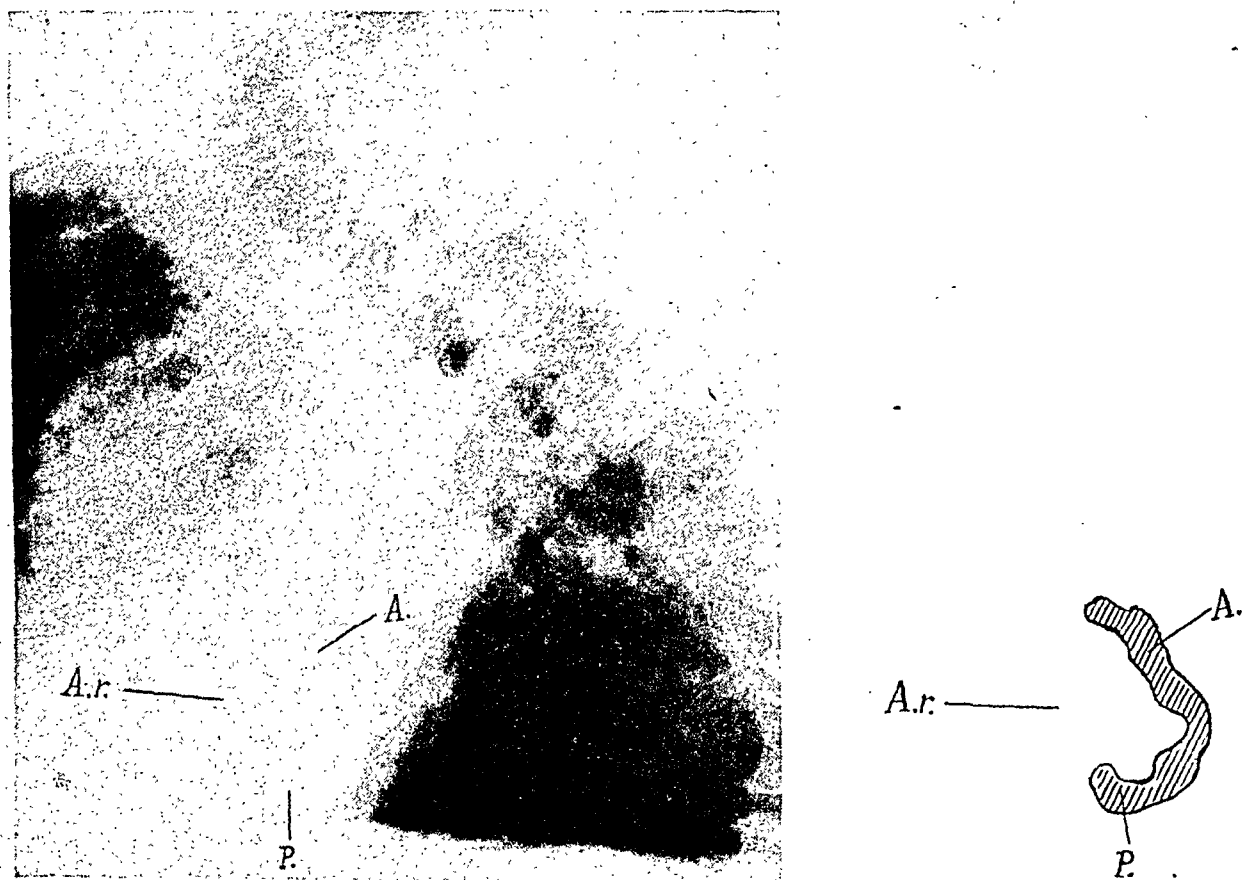


Fig. 2.—Radiographic view (left lateral) of calcified mitral annulus fibrosus with no calcifications in aortic ring (75-year-old woman with no hypertension and no cardiac symptoms). The calcium shadow is J-shaped. *P.*, posterior branch of annulus fibrosus; *A.*, anterior branch; and *A.r.*, region of the non-calcified aortic ring.

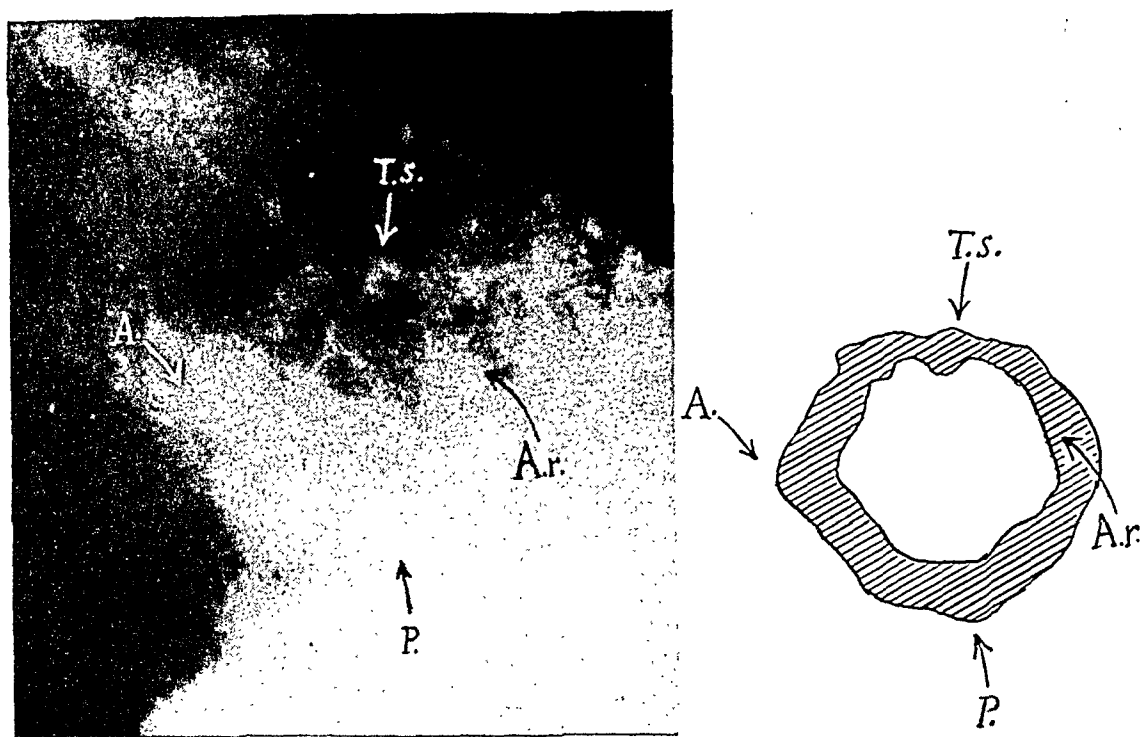


Fig. 3.—Radiographic view (right oblique) of calcified mitral annulus fibrosus with calcareous deposits in parts of the aortic ring. An 82-year-old man with compensated arteriosclerotic heart disease but no hypertension. Long, blowing diastolic murmur of aortic insufficiency. The calcium shadow is circular. *P.*, posterior branch of the annulus fibrosus; *A.*, anterior branch; *A.r.*, calcareous deposits in aortic ring; and *T. s.*, area of the left fibrous trigonum.

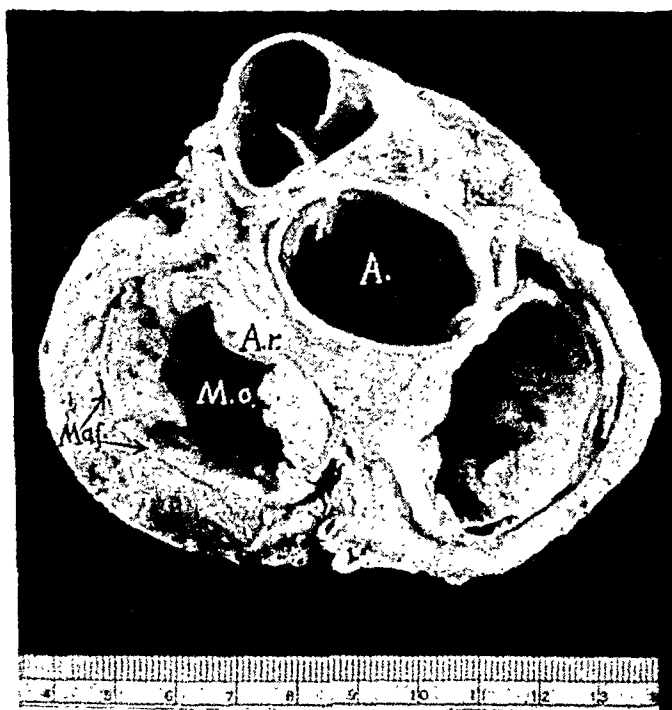


Fig. 4.—View of anatomic relationship of aorta and mitral ostium after removal of the auricles in a case of arteriosclerotic dilatation of the aorta. *M.o.*, mitral ostium; *A.*, aorta; *A.r.*, aortic ring; and *M.a.f.*, mitral annulus fibrosus. Note slight flattening of the orifice at the root of the aorta (*A.r.*). An 83-year-old man with generalized arteriosclerosis and mild hypertensive disease (blood pressure 180/100).

fluence the shape of the mitral ostium. A heart specimen in a case of arteriosclerotic dilatation of the aorta, prepared by us after removal of the auricles, shows flattening of the anteromedial portion of the mitral orifice (Fig. 4). This distortion is due to the mitral orifice adapting its shape to the expansion of the dilated aorta, which may be less marked on the specimen than it was in the lifetime of the patient, when hydrodynamic influences contributed to the widening of the aorta.

In a group of eighty-five cases of radiologically observed intracardiac calcifications, sixteen showed a completely calcified ring around the mitral ostium. In thirteen of these cases the composite calcium shadow of the annulus fibrosus and of the aortic ring was circular or ellipsoid. In three cases it was not circular, but crescentic. The greater, or posterolateral arc of the crescent, was identified as the calcified annulus fibrosus, and the lesser, or anteromedial arc, as the calcified posterolateral section of the aortic ring. These arcs were joined in the region of the calcified fibrous trigona. The rigidity and the unity of the crescentic-shaped rings were likewise noted. Deformity persisted uniformly in diastole and systole during several months of observation.

In Case 1, the appearance of the ostium is similar to that demonstrated in the specimen showing dilatation of the aorta. It is flattened on the anterolateral aspect of the ellipsoid (Fig. 5). Case 2 illustrates more advanced intrusion of the aorta, causing considerable loss of the surface of the orifice (Figs. 6 and 7). The appearance of the mitral ostium in Case 3 (Fig. 8), concerning the relationship of the annulus fibrosus to the aortic root, is similar to the foregoing observation. The amounts of lime deposit are less in this instance.

COMMENT

The radiologic demonstration was only practicable because there were extensive calcifications of both the mitral annulus fibrosus and of the aortic ring, a somewhat rare coincidence. However, protrusion of the aortic root into the mitral ostium may often take place in hypertensive disease, even though the absence of calcification prevents radiologic demonstration. The calcification itself seems not to contribute to the encroachment, only to its radiologic demonstrability. A figure of Giese,⁶ showing a radiograph of a section of the heart cut in the plane of the mitral orifice and of the adjacent part of the aortic root, illustrates such an occurrence. The mitral annulus fibrosus is calcified. The noncalcified aortic ring intrudes into the mitral orifice (Fig. 9). The author makes no note of the deformity or of the disease afflicting the patient.

A diastolic murmur was heard at the apex in each of our three cases. Whether or not this was caused by stenosis of the mitral ostium following the intrusion of the aortic root cannot be decided from these studies. Clinical and electrocardiographic investigations with sound tracings have been carried out recently along these lines by Rytand.⁷ His studies included our Cases 1 and 2 in which complete A-V block was present. According to his observations the murmur seems to follow auricular systole and is not caused by narrowing of the mitral orifice.

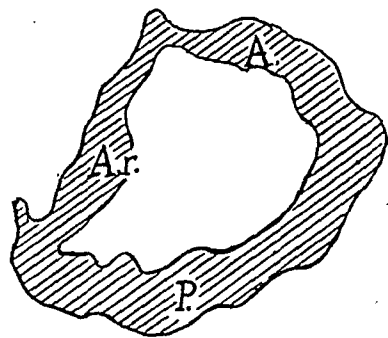
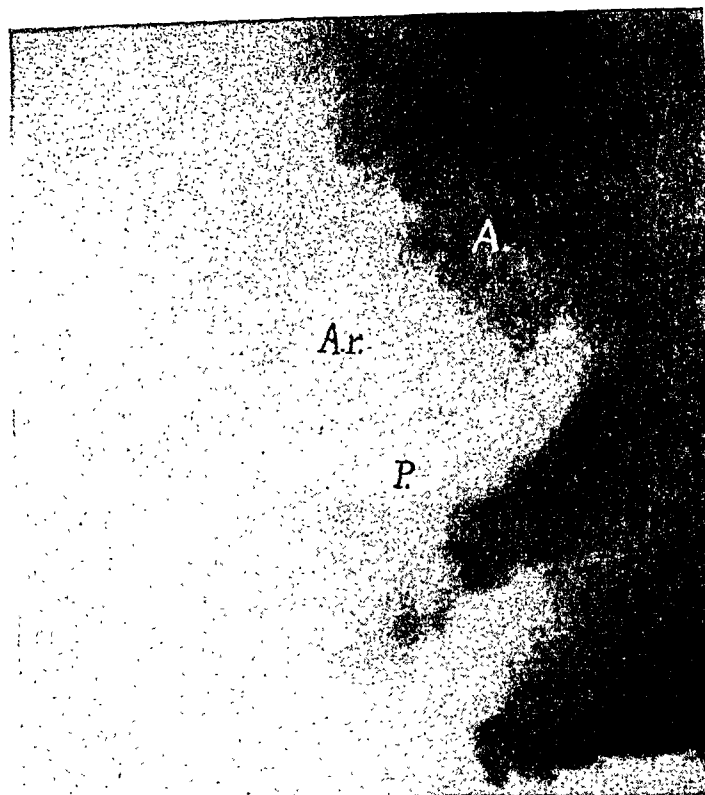


Fig. 5.—Radiographic view (left posterior oblique) of the calcified mitral annulus fibrosus and of parts of aortic ring in a case of hypertensive disease. Note considerable flattening of the mitral orifice in area of the aortic root. *P.*, posterior branch of the mitral annulus fibrosus; *A.*, anterior branch; and *A.r.*, calcareous deposits in the aortic ring. A 79-year-old woman, with moderate hypertension (blood pressure 200/90), dyspnea, coarse systolic murmur. Auricular activity during ventricular diastole (complete A-V block).

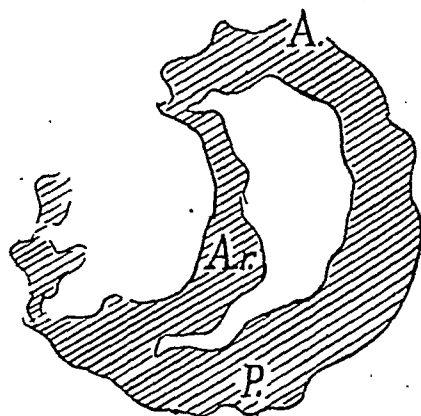


Fig. 6.—Radiographic view (left posterior oblique) of the calcified mitral annulus fibrosus and of a section of the aortic ring with intrusion of the aortic root into the mitral orifice. *P.*, posterior branch of the mitral annulus fibrosus; *A.*, anterior branch; *A.r.*, calcareous deposits in bulging (posterolateral) section of aortic ring. Calcifications in left lateral area are located in the membranaceous septum (proved by autopsy). A 72-year-old woman with advanced hypertensive disease (blood pressure 270/110), congestive failure, systolic murmur and thrill, and blowing diastolic murmur at apex, with auricular activity during ventricular diastole (complete A-V block).

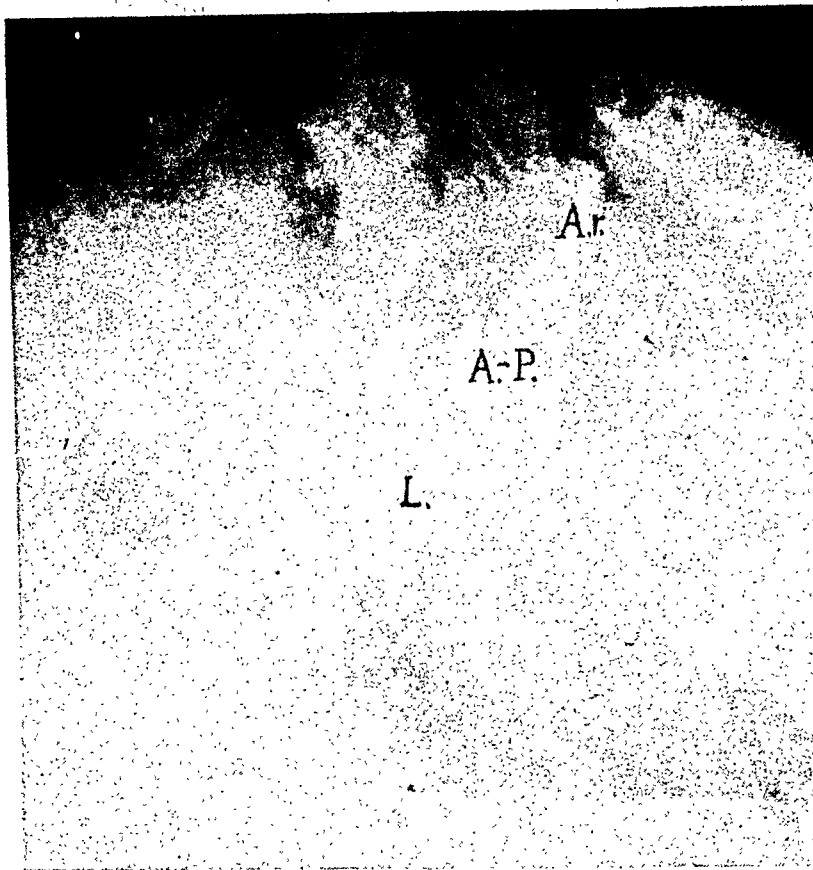


Fig. 7.—Radiographic view (right anterior oblique) of same case illustrated in Fig. 6, showing that calcifications of the mitral annulus fibrosus and of the aortic ring are in the same plane. *L.*, lateral portions of the calcified mitral ring; *A.-P.*, anterior and posterior branches of the annulus fibrosus overlying each other in this projection; and *A.r.*, bulging calcified aortic ring in the plane of the fibrosus annulus.

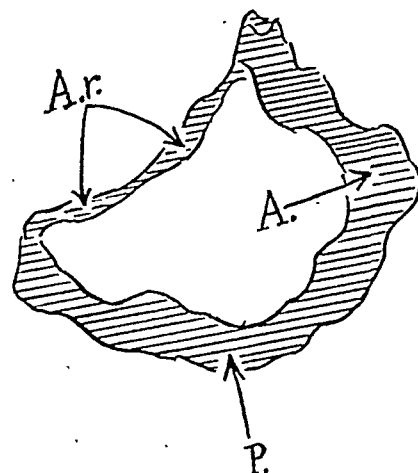
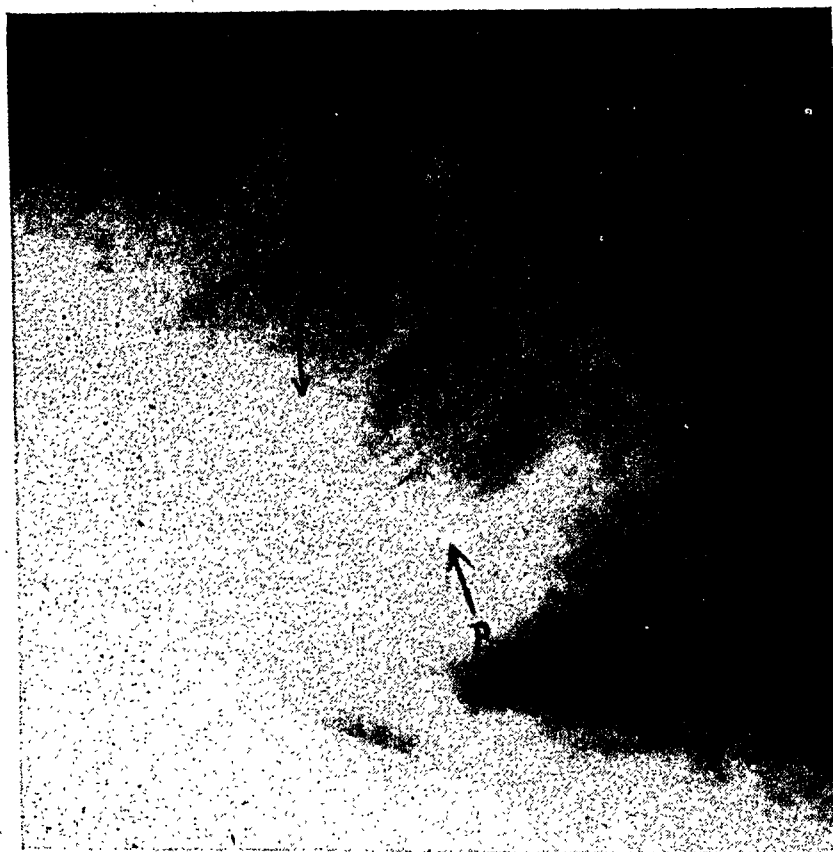


Fig. 8.—Radiographic view of the calcified mitral annulus fibrosus and of the posterolateral section of the aortic ring, bulging into the mitral orifice. *A.*, anterior branch; *P.*, posterior branch of the calcified mitral ring; and *A.r.*, calcifications in the protruding aortic ring. A 73-year-old woman with advanced hypertensive disease (blood pressure 230/105), diastolic and harsh systolic murmur. Sinus rhythm. Congestive failure, compensated.

In the same way the possibility of functional changes may be considered in the light of these findings. The narrowing of the mitral orifice must be very pronounced before it produces a significant mechanical obstacle to the circulation. Allan⁸ found that a loss of 75 per cent of the cross section of the mitral ostium reduces the inflow to the ventricle a little, and that this reduction is easily overcome by a rise of the blood pressure. In our observations the loss of the cross-section area has not reached such a degree. Assuming that the shape of the mitral orifice was, prior to the deformity, ellipsoid, and the aortic root was circular, the surface loss was estimated on the radiographs, in Case 1, as being 35 to 40 per cent, in Case 2, 50 to 55 per cent, and in Case 3, 60 to 65 per cent. It also has to be considered that the shape and size of the mitral annulus fibrosus is correlated more to the condition of the left auricle than to that of the mitral valves.⁹



Fig. 9.—Radiograph of a heart specimen cut through the mitral ostium to the plane of the atrio-ventricular ostia. *I.C.*, calcified left coronary artery; *a.*, extension of calcifications into the interventricular septum; *b.*, extension of calcifications into the aortic leaflet; *c.*, extension of calcifications into anterior portions of the myocardium; *d.*, soft tissue shadow of the noncalcified left and posterior semi-lunar valves of the aorta; *e.*, soft tissue shadow of the aortic ring bulging into the mitral ostium; *f.*, mitral ostium deformed by protruding aortic root; and *g.*, calcifications in the posterior branch of the mitral annulus fibrosus. (From Giese, W.: Verkalkungen des Herzskelettes, *Beitr. z. path. Anat. u. z. allg. Path.*, 1932.)

In cases of rigid calcifications, like those we have described, interference may be expected with the physiologic systolic reduction in the circumference of the mitral orifice. This rigidity may favor regurgitation by hindering the proper diminishing of the orifice into a narrow slit by the systolic contraction. Whether or not, in a noncalcified condition of the mitral ring, protrusion of the aorta into the mitral ostium contributes to the completeness of the systolic closure and counteracts the effects of functional dilatation of the orifice is one of the problems that remains to be solved.

Changes in the anatomic interrelationship of intracardiac structures in pathologic conditions are well known. Intrusion of the interventricular septum into the right ventricle in cases of cardiac hypertrophy¹⁰ or intrusion of the interauricular septum into the lumen of the right auricle in cases of left auricular dilatation¹¹ have often been observed. Gager¹² recorded a case of hypertensive disease in which a dissecting aneurysm of the root of the aorta encroached on the mitral ostium. In this case a loud diastolic murmur was heard. Narrowing of the mitral orifice by intrusion of the aortic root, according to available information, is not described. Its anatomic demonstration would require special autopsy technique; namely, removal of the auricles, as seen on our Figs. 1 and 4, prior to the conventional opening of the heart. Its radiologic demonstration is based on the presence of calcifications, proper fluoroscopic and radiographic technique, and analysis of the findings along the lines suggested in this article.

SUMMARY

1. Fundamentals for the radiologic demonstration of anatomic relationship of the root of the aorta to the mitral ostium in living persons, in the presence of intracardial annular calcifications, are described.

2. Three cases of hypertensive disease are presented, in which the radiologic examination showed that the root of the aorta intruded into the mitral ostium and caused loss of the cross-section area of the orifice.

3. There is indication that the aortic root may encroach on the mitral orifice also in cases of hypertensive disease, in which absence of calcifications does not permit the radiologic demonstration of these structures.

REFERENCES

1. Sosman, M. C.: The Technique for Locating and Identifying Pericardial and Intracardial Calcifications, *Am. J. Roentgenol.* 50: 461, 1943.
2. Windholz, F., and Grayson, C. E.: Roentgen Demonstration of Calcifications in the Interventricular Septum in Cases of Heart Block, *Am. J. Roentgenol.* In print.
3. Tandler, J.: *Anatomie des Herzens*, Jena, 1913, Gustav Fischer.
4. Terman, M. H., and Wolff, L.: Calcifications of the Mitral Valve, *AM. HEART J.* 31:380, 1946.
5. Martens, C.: Beziehungen zwischen den Verkalkungen des Annulus fibrosus der Mitralklappen und anderen regressiven Erscheinungen, *Beitr. z. path. Anat. u. z. allg. Path.* 90:497, 1933.
6. Giese, W.: Verkalkungen des Herzskelettes, *Beitr. z. path. Anat. u. z. allg. Path.* 89:16, 1932.
7. Rytand, D. A.: An Auricular Diastolic Murmur With Heart Block in Elderly Patients, *AM. HEART J.* 32:579, 1946.
8. Allan, D. T.: *Heart*, 12:184, 1925.
9. Fishberg, A. M.: *Heart Failure*, ed. 2, Philadelphia, 1940, Lea & Febiger.
10. Russek, H. J., and Zohman, B. L.: Bernheim Syndrome, *AM. HEART J.* 30:427, 1945.
11. Windholz, F.: Unpublished observations.
12. Gager, L. T.: Dissecting Aneurysm of Aorta Complicating Hypertension, *AM. HEART J.* 3:489, 1928.

CONGENITAL SINGLE CORONARY ARTERY IN MAN

REPORT OF NINE NEW CASES, ONE HAVING THROMBOSIS WITH RIGHT VENTRICULAR AND ATRIAL (AURICULAR) INFARCTION

JOSEPH THOMAS ROBERTS, M.D., PH.D., AND
SAMUEL DENNIS LOUBE, M.D.
WASHINGTON, D. C.

ABSENCE of one of the two main coronary arteries, with the entire heart being supplied by a congenital single coronary artery, is one of the rarest of reported cardiac anomalies that may have some practical clinical significance. Only twenty-two cases have been found in the literature, and we here report nine additional cases which we have collected. In only one of the previously reported cases were thrombosis and occlusion of the branches of the single coronary artery present with myocardial infarction of the anterior apical left ventricle; while among our adult cases there were three with myocardial infarction.

Myocardial infarction in the right ventricle is very rare, except for involvement of the small portion adjacent to an infarcted area in the left ventricle. In our Case 1 there was the association, heretofore unreported, of infarction of the posterior wall of the right ventricle and right atrium with thrombosis in the branches of a single coronary artery (the right) in a patient whose left coronary artery was absent. Electrocardiographic abnormalities could be correlated with the localization of the atrial and ventricular infarction.

Cases 1 and 2 came under our observation at Gallinger Municipal Hospital during the past year. A survey of the autopsy records of this hospital during the last five years brought to light Case 3. Six other cases (Cases 4 through 9) were found by searching the autopsy records of congenital cardiac anomalies at the Army Institute of Pathology.*

CASE REPORTS

CASE 1 (Hospital No. B97778).—A 62-year-old white man was admitted to Gallinger Municipal Hospital on Nov. 21, 1944, at 11:15 A.M. He complained of agonizing pain behind the sternum, most severe just to the right of the sternum in the fourth intercostal space. The pain, which had begun shortly after the patient had eaten some cooked ham earlier in the morning, was

From the Army Institute of Pathology and the George Washington University Division, Gallinger Municipal Hospital, and the Departments of Medicine of George Washington and Georgetown Universities' Schools of Medicine.

Presented before the Eastern Section of the American Federation for Clinical Research, Philadelphia, Dec. 8, 1945, the Washington Heart Association, Washington, D. C., Jan. 8, 1946, and the Medical Society of the District of Columbia, Sept. 30, 1946.

Received for publication Nov. 14, 1946.

*Through the courtesy of Colonel J. E. Ash, Director.

described as "a choking sensation," "cutting off my breath," and was obviously intense. He felt as though vomiting would relieve the pain. On admission to the hospital the pain was said to radiate into both arms, but this radiation was not described to other examiners a short while later. He said that he had not had similar episodes of pain, angina, hypertension, or heart disease. However, his wife said that several years previously he had had a similar but milder episode of pain in the chest. An operation for "gallstones" had been performed in 1927. No other history could be obtained.

Physical examination was limited by the acute distress and critical state of the patient. He was moderately obese; the skin was ashen grey, cold, and moist. He moaned constantly. The pulse was weak, thready, and slow, with a rate of 39 per minute. Respiration was shallow and labored, with a rate of 20 per minute. The pupils were not constricted. The lungs were free of abnormality on examination. The cardiac impulse could not be seen or felt. The left cardiac border was percussed in the anterior axillary line in the fifth intercostal space. The heart sounds were very faint or distant. There were no murmurs. The rate of the heart beat was 39 per minute, with occasional irregularities suggesting extrasystoles. The blood pressure, which had been 160/100 in the admitting office, had declined to 94/52 by the time he reached the ward. The rectal temperature was 97.0° Fahrenheit.

The urine on admission had a specific gravity of 1.020, a 3 plus reaction to the test for albumin, and three to six white cells per high power field. The blood count was as follows: hemoglobin, 15 Gm. per 100 c.c. of blood; red blood cells, 4,340,000 per c.mm.; white blood cells, 14,000 per c.mm.; differential, 75 per cent neutrophils, 4 per cent transitional cells, 19 per cent lymphocytes, 1 per cent large mononuclear cells, and 1 per cent basophiles.

The diagnosis of coronary arterial occlusion with posterior basal myocardial infarction was made and appeared to be confirmed by several electrocardiograms. He was treated with morphine, atropine, and oxygen nasally. On the day after admission he developed paralysis of the left side of the body and became completely anuric despite catheterization. On the second day after admission his rectal temperature rose to 100° F., he became cyanotic and less responsive, and numerous fine, high-pitched, musical and sibilant expiratory râles were heard throughout both sides of his chest. Left ventricular cardiac failure and possible bronchopneumonia were suspected, but before treatment for either of these complications was started, he died.

Electrocardiographic records (all properly standardized) were made on five occasions during his three days in the hospital. They were quite unique. (1) A tracing made at 11:50 A.M. on Nov. 21, 1944 (Fig. 1) showed a ventricular rate of 40 and an atrial rate of approximately 400 per minute. There was complete atrioventricular dissociation with the onset of atrial fibrillation during the recording of Lead I. Despite the changing atrial mechanism, little alteration of ventricular rhythm occurred. The R-T interval was 0.52 second. The QRS intervals were 0.10 to 0.12 second. In Lead I, the Q wave was absent, the R and S waves were equal, the S-T segment was greatly depressed (6 mm.) below the isoelectric line and sloped gradually downward from its low take-off, and the T wave was diphasic, reaching only 1 mm. above the isoelectric line in its last portion. In Lead II, a shallow Q wave (1 mm.) was present, the R wave was slurred on its descending side, and the S wave was absent. The R-T segment was broadly convex with its take-off 5 mm. above the isoelectric line. The T wave was not distinct from the R-T segment. In Lead III, the Q wave was 3 mm. in depth, the R wave again slurred on its downstroke, and the R-T segment greatly elevated with its take-off 9 mm. above the isoelectric line. The coved segment sloped upward and was continuous with the T wave, which sloped gradually down to the isoelectric line.

(2) A tracing (Fig. 2, A), taken ten minutes later with multiple precordial leads, showed essentially the same abnormalities in the three standard leads. Q waves were absent in each of the precordial leads. As the exploring electrode was moved across the chest from right to left, several important changes occurred. The R wave increased steadily in height from 1 mm. in CF₁ to more than 23 mm. in CF₆ and went off the record in CF₆. The S wave increased in depth from 11 mm. in CF₁ to 16 mm. in CF₆. Both R and S waves were slurred in each lead. The S-T take-off was depressed in each and the depth of this depression increased steadily from 2 mm. in CF₁ to 11 mm. in CF₆. The S-T segment sloped upward in Leads CF₁ through CF₆,

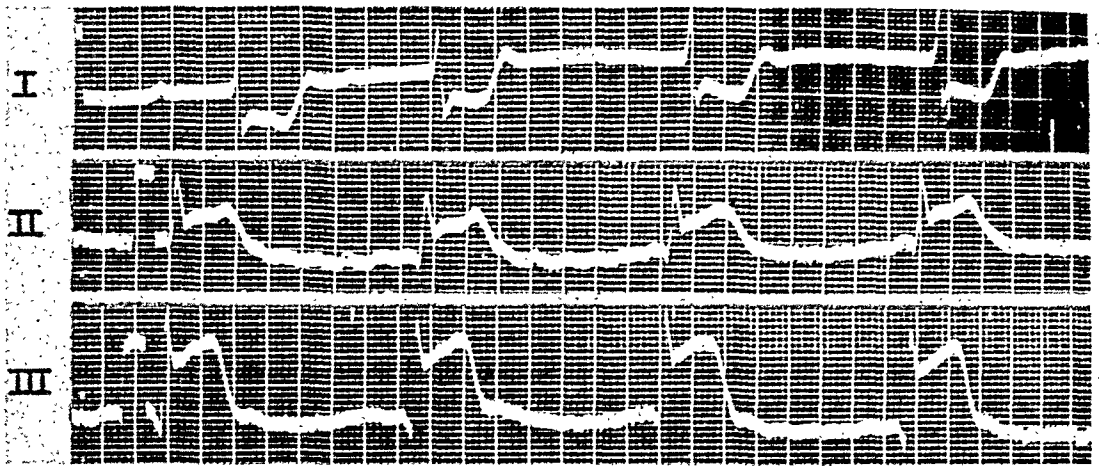


Fig. 1.—Electrocardiogram of Case 1, taken three hours after the onset of pain. Atrioventricular dissociation, with atrial fibrillation or flutter at times. See text for descriptions.

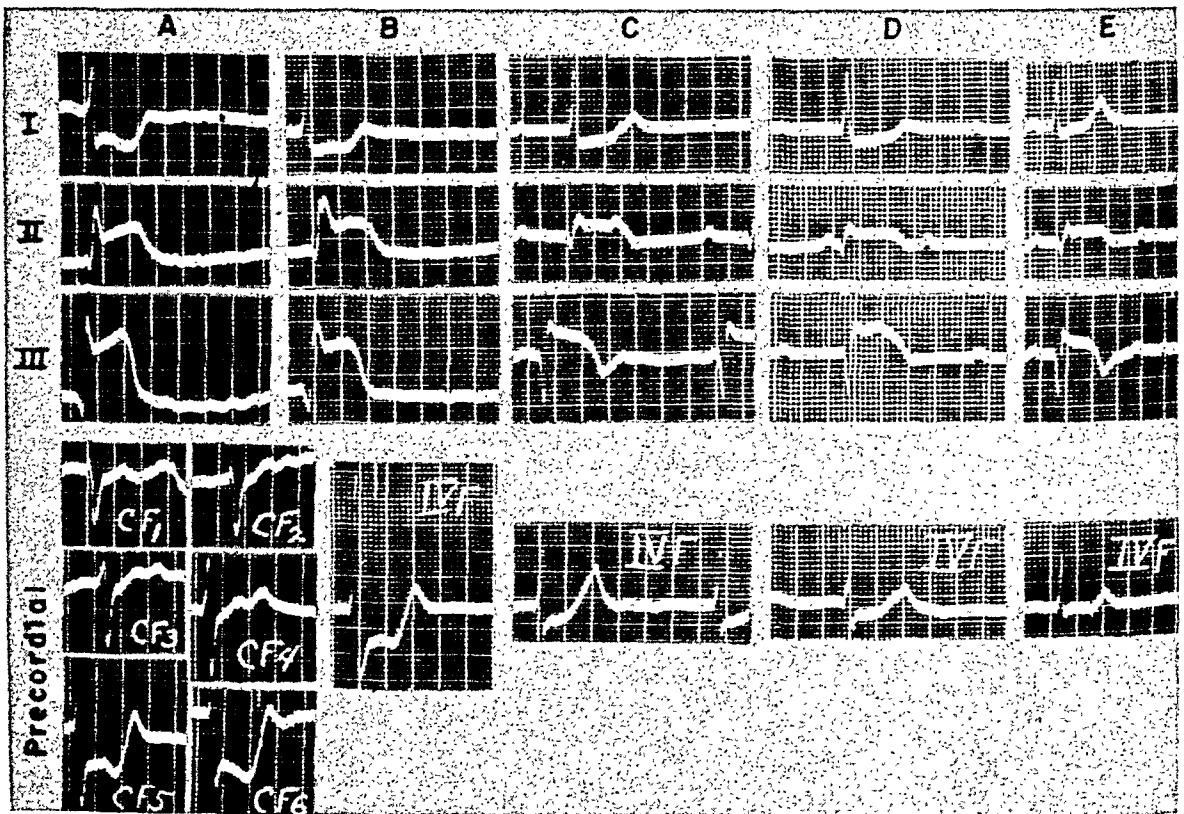


Fig. 2.—Electrocardiograms of Case 1, in sequence to emphasize rapid progress of Q_3 - T_3 type changes, atrial rhythmic changes, and variations in P waves, f waves, and P- T_A contours. A, three hours and ten minutes after onset, atrial fibrillation, with notched f waves in Lead II. Note changes in the CF leads. B, five hours after onset. C, twenty-four hours after onset. D, thirty-one hours after onset; note atrial T waves. E, fifty-one and one-half hours after onset, with elevation of P- T_A segment in Lead II. See text for description.

but in CF_6 slanted downward from the take-off. The T waves appeared to be diphasic and of low voltage in CF_1 through CF_3 , but they were obscured somewhat by the atrial deflections. In Leads CF_4 through CF_6 the T wave was diphasic, with the initial limb downward. The amplitude of T, especially of the initial inverted segment, became steadily increased with the increase in depression of the S-T segment.

(3) A tracing (Fig. 2, B) was made at 2:00 P.M. of the same day, or about two hours after the first record. The abnormalities differed only slightly from those in the previous tracings. In Lead I, the R wave was slightly higher, the S-T segment was less depressed (4 mm.) and was horizontal with a slight upward convexity instead of being sloping. In Lead II, the R wave was broadly slurred and deeply notched at its apex, the S-T segment was horizontal instead of slanting and was 5 mm. above the isoelectric line. In Lead III, the R wave was more broadly slurred, the S-T segment was again horizontal instead of slanting and was 8 mm. above the isoelectric line. Only one precordial lead was made, IVF, which may have been made with a misplaced exploring electrode because it closely resembled the previous CF_4 .

(4) Another tracing was obtained on Nov. 22, 1944, at 9:30 A.M., (Fig. 2, C). There was atrioventricular dissociation with an auricular rate of 80 and a ventricular rate of 55 per minute. P_1 and P_2 were upright, P_3 was bifid, and P_4 isoelectric. In Lead I the R wave was 10 mm. high, there being no Q waves. The take-off of the S-T segment was depressed by 2.5 mm., and sloped upward to a prominent, upright T wave. In Lead II there was a Q wave of 1 mm., with low, slurred R wave, and no S wave. The R-T segment was elevated 2 mm., and descended to an inverted T wave. In Lead III, there was a deep (9 mm.) Q wave, slurred R wave, elevated (4.5 mm.) R-T segment which sloped downward with upward convexity to an inverted, coved T wave. Lead IVF had a slurred S wave (5 mm.); the S-T segment was depressed (4 mm.) and sloped upward, and the T wave was high and peaked.

(5) Another tracing (Fig. 2, D) was taken at 4:00 P.M. of the same day, and was essentially similar to the previous one except for decreased amplitude of the T waves. "Atrial" T waves were seen clearly at times, with variation in the P- T_A interval.

(6) A sixth tracing (Fig. 2, E) was taken on Nov. 23, 1944, at 12:30 P.M., approximately fourteen hours before death. The atrioventricular dissociation persisted with a ventricular rate of 50 per minute. The P waves were unchanged. In Lead I, the S-T segment was less depressed than previously (1 mm.), and sloped upward, with upward convexity, to a prominent, upright T wave. In Lead II, the Q wave was 1 mm. in depth, the R wave was low (3 mm.) and markedly slurred. The R-T segment was elevated (2 mm.), and the T wave was inverted, with a high take-off. Lead III had a deep Q wave (6 mm.), with a slurred low R wave, an elevated R-T segment (3 mm.), and an inverted T wave. In Lead IVF, there was a small (1 mm.) S wave, the S-T segment was only slightly depressed (0.5 mm.), and the T wave was upright. Atrial P- T_A segments were elevated in Lead II.

Necropsy: The heart (Fig. 3) had the usual general shape and position. The pericardial cavity contained about 10 c.c. of clear yellowish fluid. In the epicardium over the entire right ventricle there were numerous small subepicardial hemorrhages. A reddish purple, mottled discoloration with softening and thickening was present over the posterior surface and acute margin of the right ventricle and over the lower posterior part of the right atrium. After removal and opening, the heart weighed 410 grams. The wall of the left ventricle was thickened, being about 25 mm. in its middle portion. The papillary muscles were moderately enlarged. The wall of the right ventricle was thickened, being about 15 mm. in the region of the purplish discoloration. This area, which was very soft, congested, edematous, and hemorrhagic, represented a recent myocardial infarction. The anterior apical portion of the left ventricle was somewhat lighter in color than usual and cut with slightly increased difficulty, suggesting the presence of fibrosis. The left auricular appendage was filled with firm, dark red clot which was adherent to the wall. The valves presented no abnormalities. Above the right anterior* aortic sinus of Valsalva there was the ostium (5 mm. in diameter) of the single coronary artery. Low in the left anterior aortic sinus of Valsalva was a minute shallow dimple (2 mm. in diameter and 1 mm. in depth) which

*BNA nomenclature.

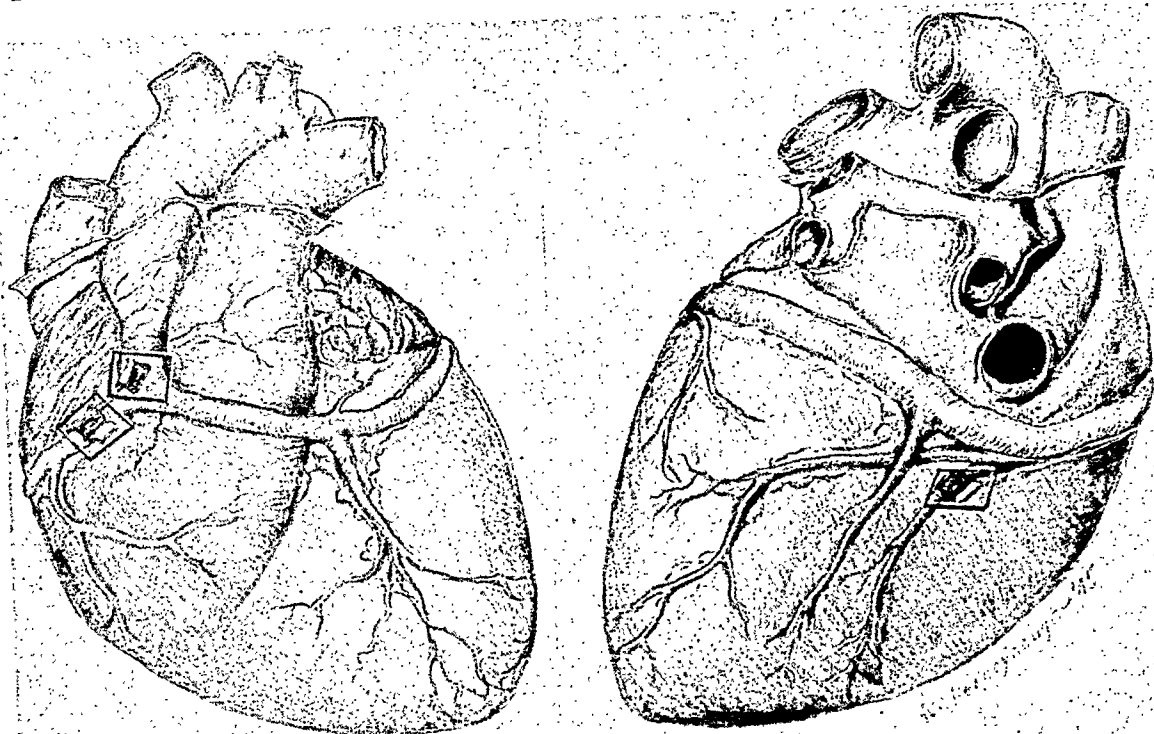


Fig. 3.—Artist's conception of the heart of Case 1, anterior and posterior views. Boxed areas indicate sites of thrombosis in the branches of the single coronary artery. Heavily shaded areas represent the infarcted portions of the right ventricle and atrium.

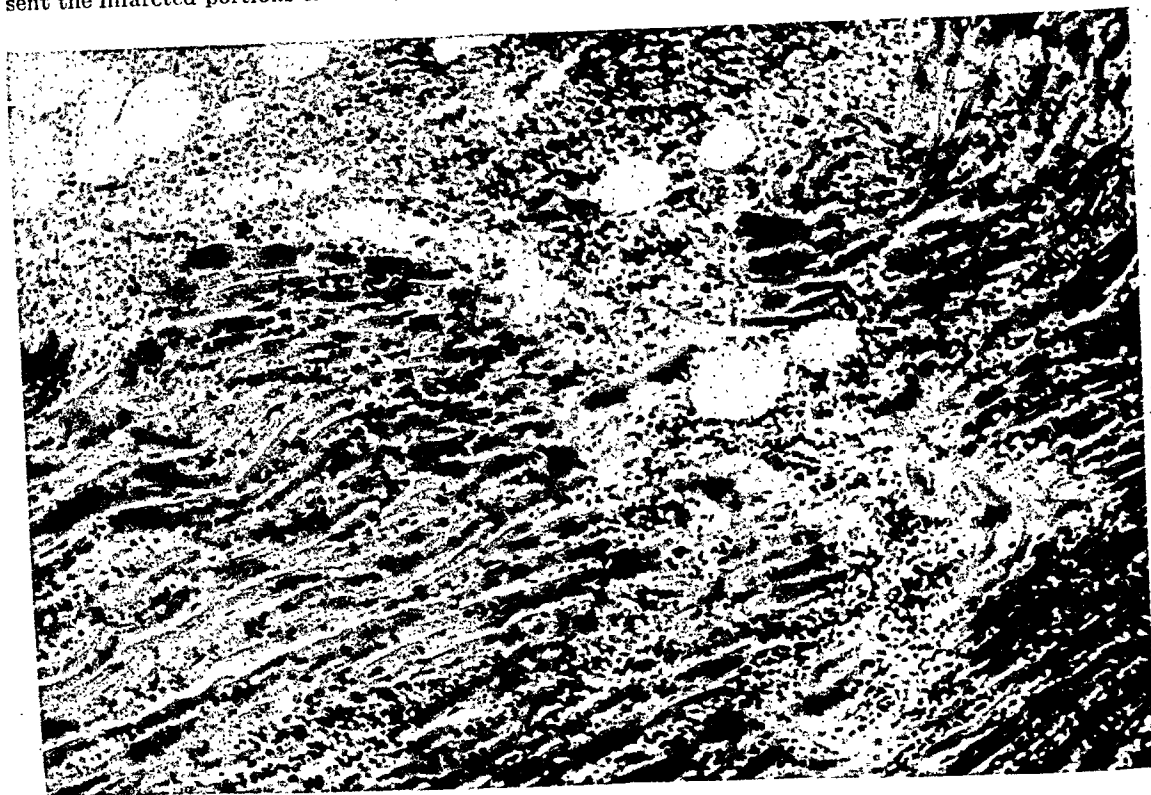


Fig. 4.—Case 1. Right ventricular infarction, recent, hemorrhagic phase; section from the acute margin of the heart. $\times 230$. (Photograph by the Army Institute of Pathology.)

on careful study was found not to be connected with any vessel. No additional openings of coronary arteries were found on close inspection of the aorta and pulmonary arteries.

A single large coronary artery was found to supply the entire heart. The coronary artery coursed anteriorly to the right between the pulmonary artery and right auricular appendage. About 1 cm. from its origin this vessel divided into two large branches, as follows: (1) A large artery which followed the course of the usual right coronary artery in the right atrioventricular sulcus to reach the posterior surface of the heart and terminate in the posterior interventricular sulcus. From this vessel several smaller branches arose in the usual positions to supply the front and back of the right atrium and ventricle. (2) An anomalous large artery which passed across the front of the conus region to assume the position of the circumflex branch of the usual left coronary artery. From this artery three important branches arose: (a) a small vessel in the position of the usual anterior descending artery (about 1 mm. in external diameter); (b) a very minute arterial twig which ran upward between the pulmonary artery and left auricular appendage to terminate just before it reached the usual site of origin of the left coronary artery; (c) a large vessel which passed in the left atrioventricular sulcus in the position of the usual left circumflex artery and gave rise to branches of the usual size supplying the lateral and posterior part of the left ventricle and atrium. Terminal branches of this vessel anastomosed with the terminal twigs of the right branch of the single coronary artery.

After the coronary arteries were opened several points of occlusion or stenosis were found, as follows: (1) A large, firm and dark red thrombus at the point of bifurcation of the single main coronary artery. This thrombus occluded the point of origin of the right branch and partly occluded the origin of the large anomalous branch which passed in front of the conus. The thrombus was firmly adherent to the endothelium which at that place was reddened, slightly elevated, and appeared to be the site of a subintimal hemorrhage. (2) A firm, dark red thrombus which almost completely occluded the lumen of the right main branch of the coronary artery midway

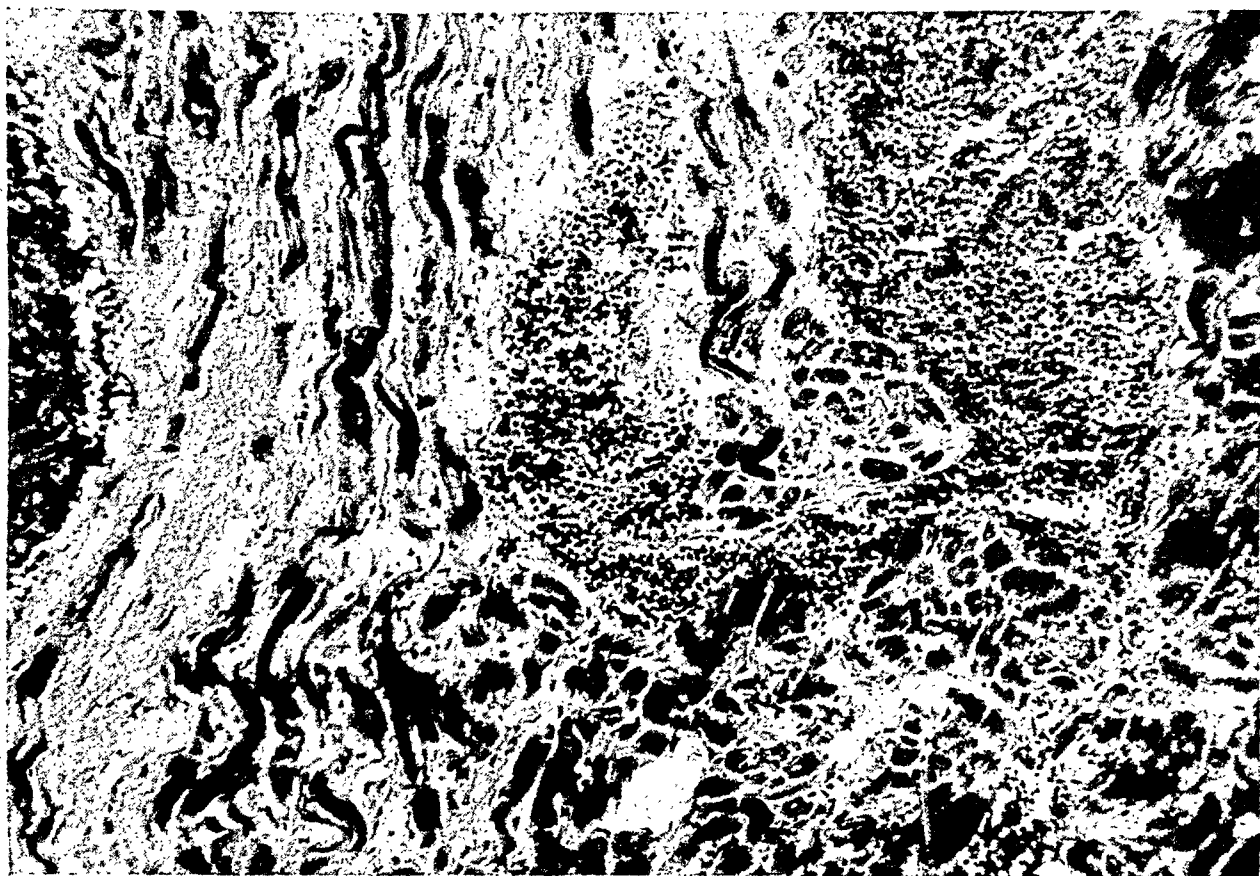


Fig. 5.—Case 1. Section from the posterior wall of the right ventricle. $\times 230$.
(Photograph by the Army Institute of Pathology.)

between its origin from the single large trunk and the acute margin of the heart. (3) A firm, dark red thrombus which completely occluded the lumen of a medium-sized branch arising from the right branch of the coronary artery just before the origin of its terminal branch in the posterior interventricular sulcus. (4) An almost complete occlusion of the thread-sized lumen of the anterior descending artery by atheromatous plaques. The coronary arteries in general were thickened and stiffened with numerous atheromatous plaques throughout their course, except for the portion in front of the region of the conus. No abnormalities of the coronary veins were found.

Sections through the recent infarction of the acute margin (Fig. 4) of the right ventricle and through the posterior surface of the right ventricle (Fig. 5) and atrium (Fig. 6) showed marked



Fig. 6.—Case 1. Right atrial infarction, recent, hemorrhagic phase; section from the posterior wall of the right atrium. x 16. (Photograph by the Army Institute of Pathology.)

swelling of the myocardial fibers, loss of normal structure, and marked differences in staining quality of the fibers. In some of these areas the myocardial fibers were much paler than usual, and the fibers were granular and fragmented. In some areas the fibers were stained darker than usual with loss of both transverse and longitudinal striations and with varying degrees of nuclear degeneration. The myocardial fibers throughout most of these sections were separated widely by masses of erythrocytes, with many polymorphonuclear and lymphocytic leucocytes. Scattered throughout these sections were occasional broad bands of fibrous connective tissue. The endocardium and epicardium in these sections were thickened, with swelling and distortion of the endothelial and mesothelial cells, disintegration of the loose fibrous connective tissue, inter-

stitial edema, and patchy extravasation of blood cells. In several places well-organized mural thrombi were seen beneath the trabeculae cordis. The myocardial fibers in the regions of these thrombi were completely distorted or had almost completely lost their structure and were separated by very marked extravasation of blood. Most of the capillaries throughout these sections were distended with blood cells. Some of the smaller branches of the coronary arteries in these sections were occluded by thrombi.

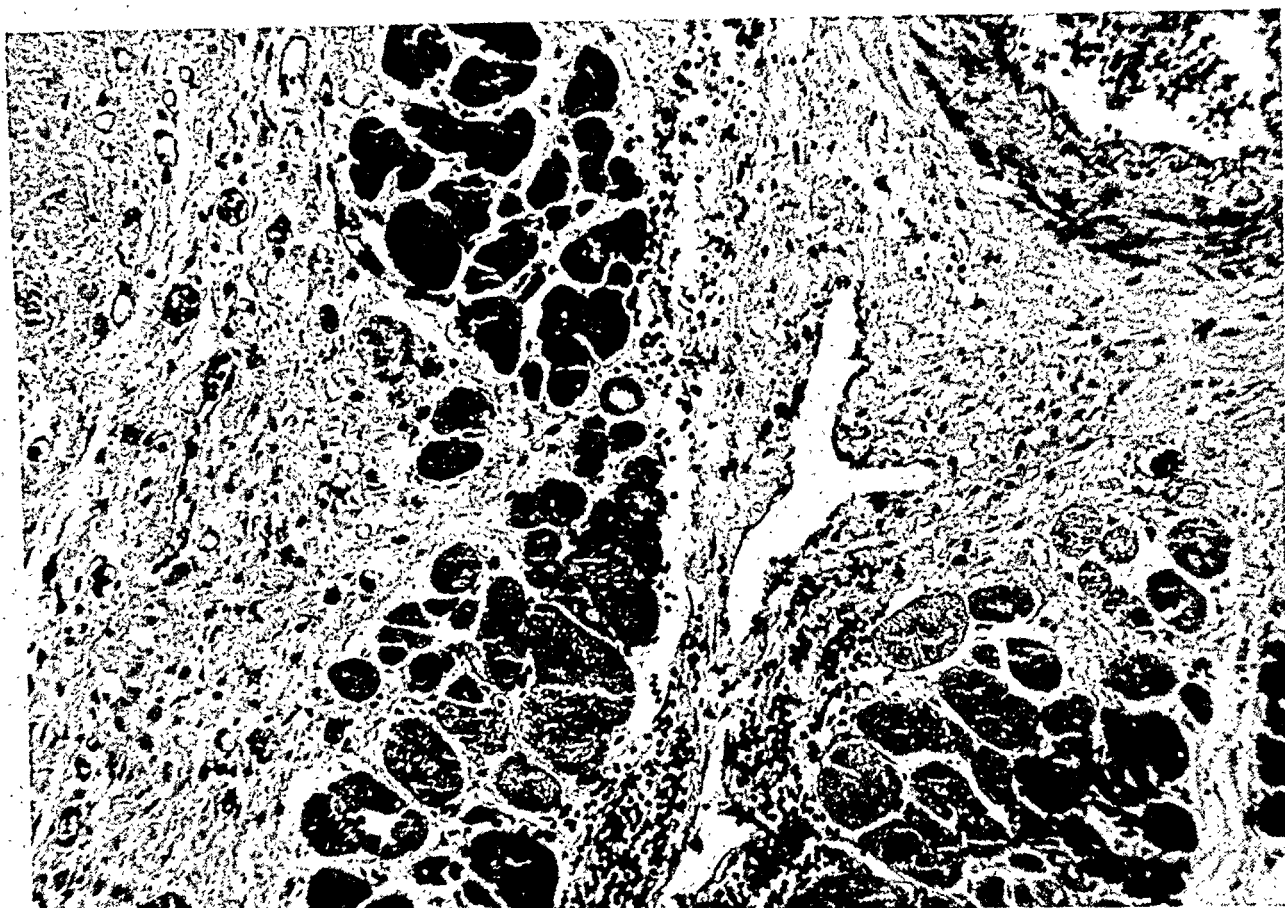


Fig. 7.—Case 1. Myocardial fibrosis; section from the anterior middle region of the left ventricle. x 230. (Photograph by the Army Institute of Pathology.)

The sections through the anterior and middle wall of the left ventricle (Fig. 7) revealed some shrinking of the myocardial fibers with proliferation of the interstitial connective tissue.

The two lungs weighed 875 grams, were poorly aerated, bluish grey in color, and firmer than usual. Pale, watery, frothy fluid oozed freely from the cut surfaces. In the lower lobes, especially on the left side, there were numerous reddish granular areas from which yellow purulent fluid could be expressed. The bronchi revealed only slight infection of the mucosa. The pulmonary vessels were not unusual. Sections of the lungs showed engorgement of the capillaries. The alveoli were filled with clear fluid, "heart failure cells," red blood cells, white blood cells, and debris in varying proportions.

The liver extended 6 cm. below the right costal margin and weighed 1,500 grams. Its capsule was smooth and pale brown. Slicing revealed a typical nutmeg appearance. There was marked congestion with dilation of the central veins, engorgement of the portal areas, and extravasation of erythrocytes. The gall bladder was absent. The two kidneys weighed 325 grams and had prominent fetal lobulation. The capsules stripped with difficulty, leaving a finely granular surface. The left adrenal was somewhat thickened and contained a cystic cavity filled with about 3 c.c. of brown fluid. Examination of other organs revealed no significant variations from normal. Permission to examine the central nervous system was withheld. The anatomic diagnosis was: Congenital anomaly of coronary arteries, thrombosis of the right branch of the single

coronary artery, infarction of the myocardium of the acute margin of the right ventricle and the posterior portion of the right ventricle and atrium, moderate hypertrophy of left ventricle, arterio-sclerosis, pulmonary edema, bilateral basal bronchopneumonia, passive congestion of the liver, and old healed scar of cholecystectomy.

CASE 2 (Hospital No. C12465).—A 42-year-old Negro laborer, was admitted to Gallinger Municipal Hospital on Aug. 21, 1945, because of prolonged and progressive weakness due to advanced pulmonary tuberculosis, and died eight days later. There were no symptoms or findings suggesting cardiac disease.

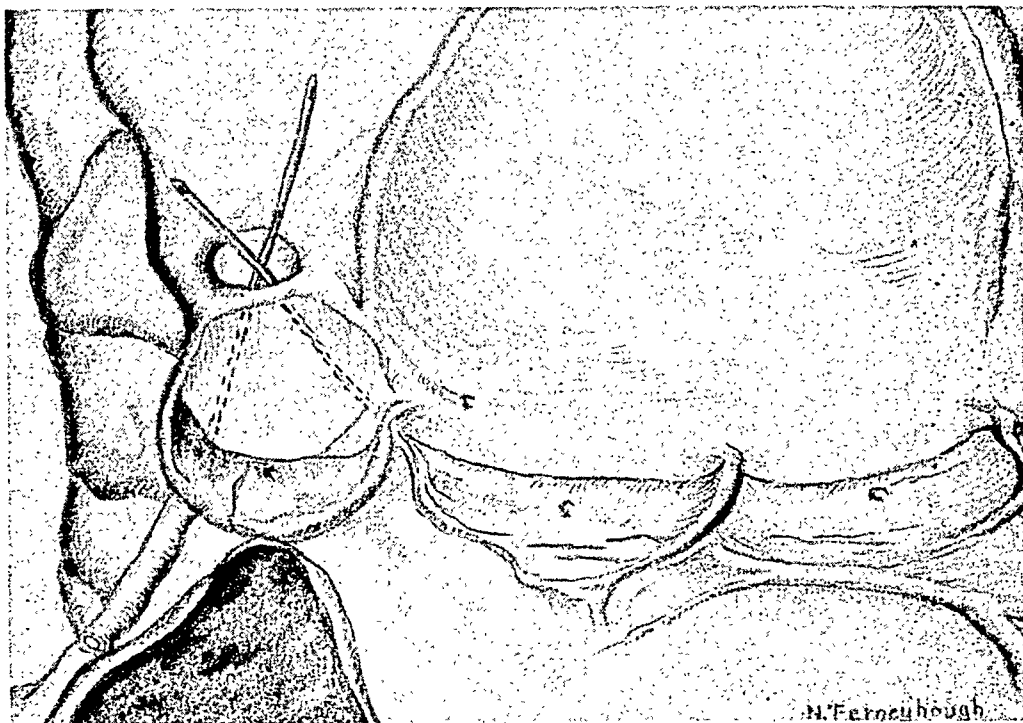


Fig. 8.—Case 2. Drawing of the single coronary artery ostium, with two needles inserted to indicate the course of the left and right main branches.

Autopsy revealed pulmonary tuberculosis, lobar pneumonia, loculated hydrothorax, thickened pleura, and fatty liver. There was only a single coronary ostium 8 mm. in diameter in the left anterior aortic sinus near the anterior commissure (Fig. 8). Five millimeters beyond the ostium, the artery divided into two branches, 4 mm. and 2 mm. in diameter. The larger branch had the usual distribution of the left coronary artery and the smaller, that of the right coronary artery. There was no evidence of another coronary arterial ostium or of any other abnormality of the heart. Several discrete atheromatous plaques were seen in the ascending aorta.

CASE 3 (Hospital E44182).—A 38-year-old Negro woman entered Gallinger Municipal Hospital on Dec. 19, 1941, with chest pain and vomiting of eleven to twelve hours' duration. She had had several previous episodes of substernal pain and dyspnea, at times associated with vomiting. The blood pressure was not obtainable, the pulse rate was 100 per minute. Short systolic murmurs were heard at the apex and tricuspid area. In spite of the administration of oxygen, morphine, and aminophyllin, the patient died thirteen hours after admission. This patient was not seen by either of us. The record was found by Dr. B. A. Fitzgerald, during an analysis of all autopsies at Gallinger Municipal Hospital in the past five years.

According to the record, "The heart weighed 300 grams. The myocardium did not appear thickened and was of good color. The aortic valve was bicuspid but not otherwise remarkable. Only the orifice of the right coronary could be detected; the left could not be found. However,

section through the myocardium showed a very small but apparently adequate coronary circulation." Microscopic examination revealed "considerable subintimal hyalinization and thrombosis in all states of organization, some areas which show swelling of the fibers, with loss of outline, and precipitation of cell constituents. In other areas this condition has progressed and there is degeneration of fibers with polymorphonuclear infiltration. In other places there is fresh scar tissue." There was microscopic evidence of syphilitic aortitis, with adventitial thickening, medial scarring, and perivascular round cell infiltration; passive congestion of lungs, liver, spleen, and kidneys; and benign adenoma of the liver.

CASE 4 (Army Medical Museum 44956).—A 46-year-old Negro soldier had had several previous hospital admissions in the ten months before his death with a diagnosis of "chronic myocarditis with cardiac decompensation." Electrocardiograms had shown progressive left axis deviation, delay of intraventricular conduction, and abnormal T waves. Before death he presented the usual picture of congestive heart failure. At autopsy he was found to have diffuse arteriosclerosis, chronic congestion of all organs, hypostatic pneumonia, and left frontal and occipital infarcts. At the tip of the left ventricle there was a large area which was only 4 mm. in thickness. The lower half of the lateral wall of the left ventricle was covered by a massive mural thrombus, and beneath this the myocardium was pale, translucent, and degenerated. There was no left coronary orifice, and the whole blood supply of the heart came from the right coronary artery. The lumen of the right coronary artery as it passed around the base of the right ventricle was markedly enlarged. The left anterior descending branch was large and showed only a moderate amount of sclerosis without constriction of the lumen. Beginning at the right coronary orifice, coursing downward and anteriorly through the base of the interventricular septum, and emptying into the anterior descending branch 4 cm. below the atrioventricular groove, there was an artery carrying the main left coronary blood supply. The left circumflex branch was medium-sized and patent. The terminal portion of the right circumflex was small. The interventricular septum just below the undefended space was pale and bloodless.

CASE 5 (Army Medical Museum 96957).—A 22-year-old white soldier died suddenly after a rapid hike. Abnormal findings at the autopsy were limited to the heart. The right heart was markedly dilated and distended with a large amount of blood. The myocardium showed no evidence of degeneration or infarction. The left coronary orifice and coronary artery were patent throughout their entire length. There was no orifice for the right coronary artery except a blind pouch, which did not lead into the right coronary artery.

CASE 6 (Army Medical Museum 106062).—A 37-year-old white soldier had had episodes of mild substernal pains at monthly intervals for two years before death. The terminal episode consisted of the usual picture of acute coronary occlusion. The electrocardiogram showed left axis deviation with elevated S-T segments in Leads I and II and inverted T₃. Autopsy disclosed hemopericardium. There was no evidence of myocardial rupture. The aortic valve was bicuspid. An aneurysm was present which opened by an oval aperture 3 mm. below the posterior aortic cusp, and it was believed that the rupture of this aneurysm had caused the hemopericardium and death. A single coronary orifice arose from the sinus of the posterior cusp. There was immediate division of the artery into the right and left coronary arteries; these vessels showed minimal atherosclerosis, and no coronary occlusion was found.

CASE 7 (Army Medical Museum 139328).—A 35-year-old white soldier complained of severe substernal pain coming on after breakfast, associated with transient loss of consciousness. He had had two previous attacks seven and five years prior to admission. The blood pressure was 92/75, and on the next day a pericardial friction rub could be heard, together with râles in the left base. On the day after admission the patient sat up in bed and suddenly fell to the floor, dead. Autopsy disclosed a large dissecting aneurysm involving the ascending and descending aorta. The aortic valve was bicuspid, and the anterior cusp was thickened, calcified, and contracted. The left coronary artery was normal in origin, branches, and distribution. The vessels were

*This case has been reported recently in another connection by L. S. Medalia and J. F. Drapiewski, *AM. HEART J.* 31:103, 1946.

patent throughout and free of sclerosis. At the site of the right coronary artery in the aorta there was an unperforated dimpling. The right side of the heart received its blood supply from a vessel which appeared to be a branch of the left circumflex coronary artery. This vessel, too, was patent and not sclerotic. The myocardium was of normal thickness.

CASE 8 (Army Medical Museum 100984).—A three-day-old white female infant, with no available history, presented multiple cardiac and extracardiac anomalies on autopsy, as follows: bicuspid aortic valve with a single coronary ostium in the right portion of the large posterior sinus of Valsalva; absence of the left coronary ostium which was represented only by a small dimple; interatrial and interventricular septal defects; anomalous arrangement of the aorta; cleft palate, harelip, talipes equinovarus, imperforate anus, accessory calcified spleens, anomalous duodenum, absence of the left kidney, ovary, and uterine tube, and paraventricular cerebral cysts. Death was attributed to atelectasis and bronchopneumonia.

CASE 9 (Army Medical Museum 100704).—A 7-day-old white male infant died of the following congenital anomalies: hypoplastic aorta, left atrium and ventricle, and mitral valve; a single coronary artery, the right, 3 mm. in diameter and patent throughout; a rudimentary dimple replacing the left coronary ostium; dilated foramen ovale; hypertrophic fetal endocarditis; patent urachus; marked fetal lobulation of kidneys; and atelectasis of the lungs.

DISCUSSION

Reports of thirty-one cases of single coronary artery are available for comparison.¹⁻¹⁹ Krumbhaar and Ehrich¹ classified fourteen cases of this type of coronary arterial anomaly into: (1) cases of absence of the right coronary artery; (2) cases of absence of the left coronary artery, including: (a) those in which the missing vessel was replaced by two branches of the right coronary artery, a septal branch, and one passing behind the aorta, and (b) those in which a septal branch only replaced the missing vessel; and (3) miscellaneous and unclassified cases of absent coronary arteries. Seven other cases of this anomaly have been found in the available literature and nine new cases are described in the present report. The salient features of these cases are indicated in Table I and Fig. 9. In these thirty-one cases the heart was nourished by a right coronary artery alone in seventeen cases, by a left coronary artery only in eleven cases; in the other three cases the identity of the single coronary artery cannot be determined from the description. The aortic sinus of Valsalva from which the single coronary artery arose was as follows: In ten cases the vessel arose from the right anterior sinus; in six, from the left anterior sinus; in seven, from the posterior sinus (which in two cases was one of a bicuspid valve); and in eight the sinus of origin was not mentioned. In seven of the cases there was a dimple and in one case a blind pouch at the usual site of origin of the missing coronary artery; five of these were instances of absence of the left coronary artery. One or both of the coronary arteries may arise from the pulmonary artery, but we have omitted such cases from this discussion.

One previously reported case and two of our cases had thrombosis of one or more branches of the single coronary artery, with infarction of the myocardium as a result. In one case myocardial "ischemia" was described. In another case there was periarterial fibrosis microscopically. In one of our cases there was myocardial fibrosis and scarring of an earlier infarction, with considerable subintimal hyalinization and microscopic thrombosis of the coronary arteries. Seventeen

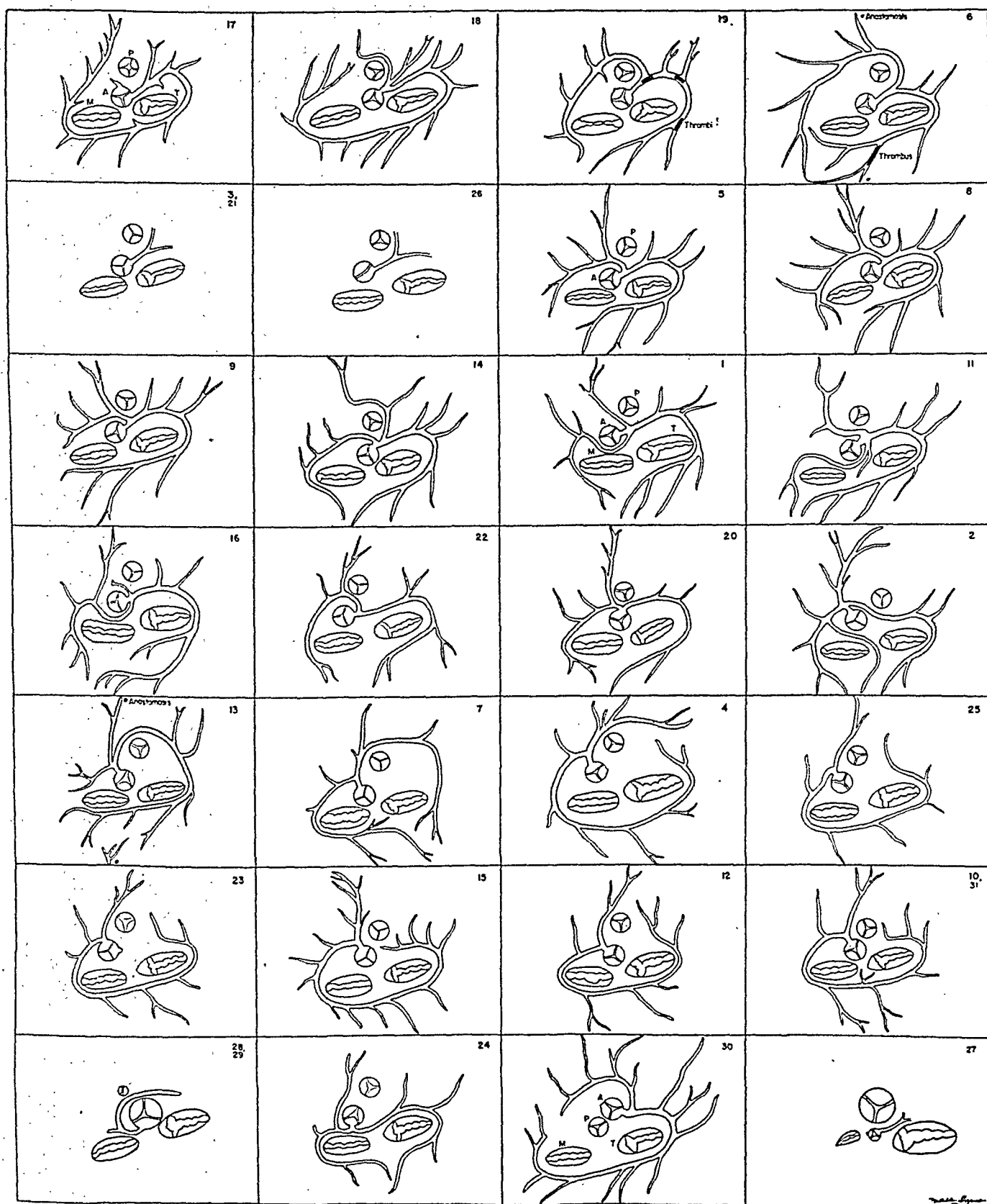


Fig. 9.—Diagrams of the pattern of the coronary arteries in the reported cases with a congenitally single coronary artery, constructed from available data. Numbered as in Table I. (Arranged in a sequence from a case with the single right artery encircling the heart, through intermediate grades of branched single arteries to a case with the single left artery encircling the heart. The cases without naming of the single artery or identification of a "posterior" sinus of origin and with other major anomalies are included.)

TABLE I. COMPARISON OF HEARTS WITH A CONGENITALLY SINGLE CORONARY ARTERY

CASE	AUTHOR, YEAR	AGE, SEX	CORONARY ARTERY PRESENT	SINUS OF ORIGIN	REMNANT OF ABSENT CORONARY ARTERY	THROMBUS	OTHER CARDIAC DISEASE OR ANOMALY	CAUSE OF DEATH
1	Bochdalek, 1867 ²	60-F	R	Right	—	—	Chronic mitral and aortic endocarditis	Chronic mitral and aortic endocarditis
2	Engelman, 1897 ³		L	?	—	—	—	Unstated
3	Garaud, 1909 ⁴	39-F	R	Posterior	—	—	Ischemia	Bronchitis, congestion, angina
4	Plaut, 1922 ⁵	37-M	L	?	Brown dimple in rt. sinus	—	Endocarditis lenta	Endocarditis lenta
5	Gallavardin and Ravault, 1925 ⁶	45-F	R	Rt. ant.	—	—	Chronic mitral and aortic endocarditis	Chronic mitral and aortic endocarditis
6	Smith and Graber, 1926 ⁷	46-M	R	?	—	—	Anat. and lat. infarct	Coronary occlusion, congestive heart failure
7	Petren, 1930 ⁸	46-M	R	?	—	—	—	Apoplexy
8	Kintner, 1931 ⁹	33-M	L	Left	—	Descending branch	Chronic mitral and aortic endocarditis	Pneumonia, renal insufficiency (postoperative)
9	Born, 1933 ¹⁰	65-M	R	Rt. ant.	—	—	—	Empyema, gangrene of lung
10	Kochel, 1934-35 ¹¹	54-M	R	Rt. ant.	—	—	—	Pneumonia, early bicuspid endocarditis
11	Sanes, 1937 ¹²	39-F	L	Left	—	—	Early bicuspid endocarditis	Acute glomerulonephritis, toxic myocarditis
		4-M	R	Rt. ant. (4 openings in common orifice)	Dimple ant. aortic sinus near commissure between cusps	—	Recent interstitial myocarditis	

		Richter (Case I), 1937 ¹³	63-M	L	Left (higher than usual)				Cancer of stomach
12		Richter (Case I), 1937 ¹³	Adult	L	?	—	—	—	Unstated
13		Richter (Case II), 1937 ¹³	61-M	R	Rt. ant. ?	—	—	—	Cerebral hemorrhage
14		Speer, 1938 ¹⁴	44-F	L	Left. ant.	—	—	Enlarged heart and chronic thickened mitral valve	Pulmonary embolism, thickened mitral valve
15		Krumbhaar and Ehrich (Case I), 1938 ¹	35-F	R	Rt. ant.	—	—	Fine periarterial fibrosis	Cancer of uterus
16		Krumbhaar and Ehrich (Case II), 1938 ¹	42-F	R	Posterior	Small branch running up between pulmonary artery and aorta, ending blindly	—	Acute rheumatic carditis. Quadricuspid pulm. valve. Anomalous rt. subclavian artery	Acute rheumatic carditis
17		Maddox and Isbister, 1940 ¹⁵							
18		King, 1940 ¹⁶	45-M	R	Rt. ant.	—	—	Left ventricle thickened and somewhat dilated	Lobar pneumonia
19		Roberts and Loube, Case 1	62-M	R	Rt. ant.	Dimple left ant. sinus. Minute artery twig between pulmonary artery and left auricular appendage	3	Myocardial infarction. Numerous atheromatous plaques in cor. arteries	Myocardial infarction, of right ventricle wall and right atrium. Congestive failure
20		Roberts and Loube, Case 2	42-M	L	Left ant.	—	—	—	Pulmonary tuberculosis, lobar pneumonia
21		Roberts and Loube, Case 3	38-F	R	?	—	Yes, microscopically	Myocardial infarction. Syphilitic aortitis, bicuspid aortic valve	Coronary occlusion, myocardial infarction
22		Roberts and Loube, Case 4	46-M	R	?	—	—	Myocardial infarction, apical, lateral	Congestive heart failure, myocardial infarction
23		Roberts and Loube, Case 5	22-M	L	Left	Blind pouch	—	Acute dilatation of rt. heart	Acute dilatation of rt. heart on unusual exertion

TABLE I. COMPARISON OF HEARTS WITH A CONGENITALLY SINGLE CORONARY ARTERY—(CONT'D)

CASE	AUTHOR, YEAR	AGE, SEX	CORONARY ARTERY PRESENT	SINUS OF ORIGIN	REMNANT OF ABSENT CORONARY ARTERY	THROMBUS	OTHER CARDIAC DISEASE OR ANOMALY	CAUSE OF DEATH
24	Roberts and Loubé, Case 6	37-M	Divides into L and R.	Posterior	—	—	Bicuspid aortic valve, aneurysmal sac opening below posterior aortic cusp	Rupture of aneurysmal sac, hemopericardium
25	Roberts and Loubé, Case 7	35-M	L	?	Unperforated dimpling at site of rt. cor. artery	—	Bicuspid aortic valve, anterior cusp thickened, calcified, contracted	Dissecting aneurysm
26	Roberts and Loubé, Case 8	3-F	R	Posterior	Dimple	—	Bicuspid aortic valve, atrial and ventricular septal defects	Atelectasis broncho-pneumonia. Multiple extracardiac anomalies
27	Roberts and Loubé, Case 9	7-M	R	Rt. ant.	Dimple	—	Hypoplasia of left ventricle, mitral valve, atrium, aorta, dilated foramen ovale	Congenital heart disease, patent urachus, atelectasis.
28	Monckeberg, Case I, 1924 ¹⁷	5-M	?	Posterior	—	—	Bicuspid pulmonary valve, tetralogy of Fallot	Unstated
29	Monckeberg, Case II, 1924 ¹⁷	—	?	Posterior	—	—	Same	Unstated
30	Ngai, 1935 ¹⁸	53-F	R	R. posterior	Dimple	—	Septal defects; transposition of aorta and pulmonary artery, rt. aortic arch, sinistroposition of rt. auricle	Atelectasis and pneumonia
31	Ravin and Geever, 1946 ¹⁹	—	L	?	—	—	—	"Extracardiac"

of the patients were males, nine were females, and the sex in the other two was not mentioned. The age of the twenty-six patients in whom this information was given ranged from 3 days to 68 years; on exclusion of the four children, the average age of these patients was 45 years. Four of the hearts had bicuspid aortic valves, and in one case there was a quadricuspid pulmonary valve. Six cases had other significant congenital cardiac anomalies.

Two of the hearts showed chronic mitral and aortic endocarditis; in one there was endocarditis lenta; and in another heart there was early endocarditis of a bicuspid aortic valve. One heart showed a "chronically thickened mitral valve," and in one of the instances of bicuspid aortic valve the anterior cusp was thickened, calcified, and contracted. In one heart there was recent interstitial myocarditis, and in one acute rheumatic carditis. In one of our cases there was acute dilatation of the right heart, with no other abnormality aside from the single coronary artery.

The cause of death in each of the cases was probably unrelated to the congenital anomaly of the coronary artery with the six following possible exceptions. In the case of Smith and Graber,⁷ as in our Cases 1, 3, and 4, the anomalous coronary arteries may have prevented the utilization of anastomatic vessels to relieve the ischemia of the myocardium following thrombosis of the coronary arteries. Similarly, the angina and heart failure occurring in Garaud's⁴ case may have been related to the ischemia observed histologically and might have been due to the lack of availability of compensatory anastomoses. However, the well-known frequency of myocardial ischemia and infarction in patients in the same age range as in these cases (38 to 62 years) diminishes the likelihood that the congenital anomaly alone was the main factor causing death. In our Case 5, the presence of acute dilatation of the right heart, associated with absence of the right coronary artery, suggests a possible casual relationship. In the other patients in this series who had some type of cardiac disease, such as endocarditis, other congenital cardiac anomalies, or rheumatic carditis, the congenital anomaly of the coronary arteries had no evident significance. In the other cases death was due to factors unrelated to the heart.

Case 1 of our series presented several unique features which were not present in any of the other cases. The infarction of the myocardium involved the larger portion of the wall of the right ventricle and a small portion of the atrium. An infarction of the right ventricle following occlusion of the coronary arteries is an extreme rarity²⁰ except in the small portion adjacent to the septum. This common observation has given rise to much speculation. Whitten²¹ believed that the rarity of right ventricular infarction was related to anatomic differences in the angle with which the penetrating branches arose from the main coronary arteries in the two ventricles. He thought that the more obtuse angle with which the perforating branches arose in the right ventricle resulted in less sharp bending of these perforating arteries in the right ventricle, whereas the sharper angle of origin in the left ventricle gave rise to more traumatic bending during systole and predisposed to arterial degeneration. Others, since the time of Vieussens and Thebesius, have thought that the wall of the right ventricle was so thin that it might be adequately nourished by the so-called Thebesian, or luminal vessels,

whereas the wall of the left ventricle was so thick that only a thin portion next to the endocardium could be nourished by these channels. Some experimental basis for this belief has been established by Wearn²² and Roberts.²³

Recently Blumgart, Schlesinger, and Davis²⁴ called attention again to the importance of the intercoronary anastomoses as a source of blood supply for an area supplied by an occluded coronary artery. They found by studying careful injections that myocardial infarction might not occur following occlusion of one coronary artery until a subsequent stenosis or occlusion involved another coronary artery from which compensatory anastomoses had arisen. In our Case 1 this factor may have been very important in leading to the infarction, for the anterior descending coronary artery was already seriously stenosed by longstanding atheromatous changes and so could not serve as a source for supplying the myocardium normally nourished by the thrombosed right coronary artery. Furthermore, it seems quite likely that all the available intercoronary arterial anastomoses had been dilated greatly and utilized long before the coronary artery thrombosis occurred to compensate for the defect in distribution of the coronary arteries during early embryonic life.

In each of the four cases of myocardial infarction, and in each of the three instances of myocardial fibrosis or ischemia, the absent vessel was the left coronary artery. This finding may indicate that better compensation for an absent coronary artery is made when the single persisting vessel is the left coronary artery rather than in the converse situation. This supports a belief that an intact arterial supply is more essential for the thicker left ventricle than for the thin right ventricle.

Infarction of the auricular muscle has seldom been described. The same conditions exist in the thin auricular muscle which have been used to explain the rarity of right ventricular infarction. Since the experimental and clinical observations of Cushing, Feil, Stanton, and Wartman²⁵ it has become recognized that infarction of the auricle may occur and be suspected from electrocardiograms occasionally. The location of the atrial infarction in our Case 1 was very likely such as to involve the atrioventricular node and bundle also. Involvement of this specialized conduction tissue was probably the mechanism producing the complete atrioventricular block and dissociation which was recorded electrocardiographically. Careful correlation of the electrocardiographic and anatomic abnormalities of this case makes it appear to be a close analogy to experimental conditions where atrioventricular block is produced prior to injury of atrial or auricular muscle. Miller and Perelman²⁶ recently (since our case has been described in abstract²⁷) have discussed somewhat similar electrocardiographic abnormalities in a patient on whom an autopsy was not performed. In the light of these earlier studies, our Case 1 seems to establish the following signs as grounds for suspecting future atrial infarctions: (1) atrial arrhythmias, especially if changing rapidly in type; (2) atrioventricular block; (3) changing contour of P or f waves; (4) changing contour of the P-T_A segment or interval and of the atrial T wave (T_A), if evident, as it may be with dissociation or prolonged P-R intervals. Precordial records, especially of the CF₁ or CF₂ positions or esophageal leads, might be expected to yield more information on this point

in suitable patients. Additional experimental and clinical studies on this important problem would be of interest. The atrial arrhythmia which varied from tachycardia to flutter and fibrillation was probably due to the ischemia of the atrial muscle, as were the changes in the atrial T waves, in *f* or P-wave contour, and P-T_A segments and intervals.

Another unique feature of this case was the presence of a probable subintimal hemorrhage at a point of thrombosis of the single coronary artery. Such lesions have been emphasized by Wartman,²⁸ Paterson,²⁹ Winternitz and co-workers,³⁰ and others as the basis for coronary thrombosis in some cases. Although the sections through this area were lost, gross inspection indicated the probability of subintimal hemorrhage.

The serial electrocardiograms obtained during the terminal illness of our first patient were quite unusual. We have been unable to find any report of exactly similar records. The magnitude of the deflection of the S-T segments was much greater than in any case of posterior basal myocardial infarction known to us. The use of multiple precordial leads made these records of even more value. The mode of death of this patient was readily explained as being due to acute congestive heart failure after loss of function of much myocardial tissue, pulmonary edema, terminal bronchopneumonia, and cerebral arterial occlusion by an embolus arising from the mural thrombus.

Our second case showed no evidence of coexisting cardiac disease, death being due to an entirely unrelated illness, and well exemplifies the possible compatibility of this anomaly with normal existence.

Although it cannot be established except by speculation, the possible mechanisms by which anomalies of the coronary arteries arise, as in these cases, are as follows: (1) absence of the anlage for one coronary artery; (2) a displacement of the anlage of one coronary artery so that it fuses with the anlage of the other; or (3) occlusion by thrombosis, infection, or maldevelopment of one coronary artery soon after its formation, with failure of subsequent canalization and with compensatory dilatation of the remaining vessels. In our Case 1 it seems most probable that the third mechanism occurred. In this case there is good reason to believe: (1) that the coronary arteries originally arose with a normal pattern, and (2) that soon afterward occlusion of the trunk of the left coronary artery occurred with subsequent degeneration of the connection between the tiny dimple at the site of the usual left coronary ostium and the tiny threadlike artery arising from the anomalous vessel in front of the conus and running upward between the pulmonary artery and left auricle. (3) As a result of this, the usually minute vessels connecting the right and left coronary arteries in front of the conus became dilated to form the anomalous large branch arising from the single coronary artery. This mechanism might similarly be invoked in the case of Maddox and Isbister,¹⁵ who described a small branch running up between the pulmonary artery and the aorta, which they believed was the remnant of the origin of the normal left coronary artery. In their case, however, no aortic dimple was described. Because, according to this speculation, the intercoronary anastomoses had been dilated since early embryonic life, there was less possibility for com-

pensatory dilatation of anastomoses to occur after the occurrence of coronary thrombosis.

A displacement of the anlage of the "missing" coronary artery would seem to be the most common mechanism. Our Case 2, in which the common trunk divided 5 mm. beyond the ostium into two branches corresponding to the right and left coronary arteries, might represent a displacement of the anlage to a point just beyond the origin of the "single" coronary artery. Kintner's⁹ case is representative of a group of cases in which the "absent" left coronary artery is replaced by a branch of the right coronary artery which passes to the left between the aorta and pulmonary artery and passes through the septum to the anterior surface. Kintner,⁹ Sanes,¹² and Speer¹⁴ refer to the abnormality in their cases as "anomalous origin of the left coronary artery" rather than as "absent coronary artery" and, in a sense, rightly so.

Brown³¹ states that the anlagen of the coronary arteries appear about the fourteenth day of fetal life, the left being formed before the right, and that they appear in the truncus arteriosus before that structure is divided by the spiral septum. An aberration in the site of division by the septum might account for anomalous origin of one or both coronary arteries from the pulmonary artery; twenty-one such cases have been reported, according to Soloff.³² It is conceivable that a dorsal deviation of the septum, which is formed from the lateral cushions of the truncus arteriosus, could crowd the anlage of the left coronary artery toward the right so that the two anlagen fused. After the subsequent counter-clockwise rotation of the dividing truncus arteriosus, the anomalous left branch of the fused anlagen might pass between aorta and pulmonary artery, and penetrate the septum. Similarly, inclusion of an unusually large part, or all, of the right lateral cushion into the ventral (or pulmonary artery) division of the truncus arteriosus might result in a bicuspid aortic valve, which occurred in three cases, or a quadricuspid pulmonary valve, which was observed in one case.

Hyrtil³³ has stated that to identify this type of anomaly as a true case of absent coronary artery it must be proved that the single artery present really supplies the entire heart. By only the first of the above named mechanisms could this postulate be fulfilled, namely, by an absent coronary arterial anlage.

The group of cases exemplified by that of Petren⁸ and the first case of Krumbhaar and Ehrich,¹ in which the right coronary artery was absent (the right heart being supplied by a continuation of the circumflex branch of the left coronary artery) would seem to conform to the Hyrtl postulate, in that one artery apparently supplies the whole heart. Similar cases are those of Koche¹¹ and of Richter,¹³ and our Case 7. In Plaut's⁵ case the right heart was supplied by a large branch from the anterior descending branch of the left coronary artery, but the small brown dimple in the aorta at the usual site of the right coronary ostium may have represented an anlage which had failed to develop. Since, in the larger proportion of the cases, this is not the mode of substitution for the missing coronary artery, we feel that Hyrtl's postulate need not determine the identification of cases with only one coronary artery, and that this group of

anomalies should be identified as the origin of the coronary arterial circulation from a single trunk rather than as a true congenital absence of one coronary artery.

SUMMARY

Nine new cases of absence of a coronary artery are added to twenty-two previously reported cases of this anomaly. Three of these nine patients had occlusion at one or more points of the single coronary artery, with resultant myocardial infarction.

One patient had massive infarction of the right ventricle and auricle, and a unique series of electrocardiograms was recorded. These indicate that atrial infarction should be suspected with the occurrence of: (1) atrial arrhythmias, especially if changing rapidly in type; (2) atrioventricular block; (3) changing contour of P or f waves; (4) changing contour of the P-T_A segment or interval and of the atrial T wave (T_A) if evident, as it may be with dissociation or prolonged P-R intervals.

The embryologic and clinical features of the anomaly are discussed and mechanisms for its production are propounded. This anomaly is compatible with normal cardiac function, but adds extra hazard in the presence of coronary artery disease because the available collateral anastomoses must be utilized early in life.

REFERENCES

1. Krumbhaar, E. B., and Ehrlich, W. E.: Varieties of Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies, *Am. J. M. Sc.* 196:407, 1938.
2. Bachdalek, H.: Anomaler Verlauf der Krauzarterien des Herzens, *Virchows Arch. f. path. Anat.* 41:260, 1867.
3. Engelman, G.: Ein Fall von Mangel einer Coronararterie, *Anat. Anz.* 14:348, 1898.
4. Garaud: Un Cas de Malformation Congenitale des Arteries Coronaires; Mort Subite, *Marseille Med.* 46:82, 1909.
5. Plaut, A.: Versorgung des Herzens durch nur eine Krauzarterie, *Frankfurt Ztschr. f. Path.* 27:84, 1922.
6. Gallavardin, L., and Revault, P.: Anomalie d'origine de la Coronaire Arterieuse, *Lyon méd.* 136:270, 1925.
7. Smith, F. M., and Graber, V. C.: Coronary Thrombosis With Congenital Absence of the Left Coronary Artery, *Arch. Int. Med.* 38:222, 1926.
8. Petren, T.: Ein Fall von Mangel der A. Coronaria Cordis Dextra, *Virchows Arch. f. path. Anat.* 278:158, 1930.
9. Kintner, A. R.: Anomalous Origin and Course of the Left Coronary Artery, *Arch. Path.* 12:586, 1931.
10. Born, E.: Ueber Missbildungen der Krauzarterien und ihre Beziehungen zu Zirkulationsstörungen und plotzlichen Tod, *Virchows Arch. f. path. Anat.* 290:688, 1933.
11. Kockel, H.: Eigenartige Kranzschlagadermissbildungen, *Beitr. z. path. Anat. u. z. allg. Path.* 94:220, 1934.
12. Sanes, S.: Anomalous Origin and Course of the Left Coronary Artery in a Child, *AM. HEART J.* 14:219, 1937.
13. Richter, O.: Ueber das Fehlen einer Krauzarterie, *Virchows Arch. f. path. Anat.* 299:637, 1937.
14. Speer, F. D.: Anomalous Origin and Course of Left Coronary Artery in Adult, *New York M. Coll. & Flower Hosp. Bull.* 1:201, 1938.
15. Maddox, K., and Isbister, J.: Case of Single Coronary Artery, Quadricuspid Pulmonary Valve and Anomalous Right Subclavian Artery: Death From Acute Rheumatic Carditis, *M. J. Australia* 1:50, 1940.
16. King, E. S. J.: Single Coronary Artery, *Brit. Heart J.* 2:79, 1940.

17. Monckeberg, J. G., In Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, vol. 2, Berlin, 1924, Springer-Verlag, p. 155.
18. Ngai, S. K.: Congenital Anomaly of the Heart, *Am. J. Path.* 11:309, 1935.
19. Ravin, A., and Geever, E. F.: Coronary Arteriosclerosis, Coronary Anastomoses and Myocardial Infarction, *Arch. Int. Med.* 78:125, 1946.
20. Fishberg, A. M.: *Heart Failure*, ed. 2. Philadelphia, 1940, Lea & Febiger.
21. Whitten, M. B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, *Arch. Int. Med.* 45:383, 1930.
22. Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation, *Harvey Lect.* 35:243, 1939-40.
23. Roberts, J. T.: The Role of the Small Vessels and Nerves of the Heart in Heart Failure, Coronary Artery Thrombosis and Cardiac Pain, *M. Ann. District of Columbia* 16:483, 1945. (The Davidson Lecture.)
24. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathological Findings, *AM. HEART J.* 19:1, 1940.
25. Cushing, E. H., Feil, H., Stanton, E., and Wartman, W. B.: Infarction of the Cardiac Auricles (atria), *Brit. Heart J.* 4:17, 1942.
26. Miller, R., and Perelman, J. S.: Multiple Disturbances of Rhythm and Conduction and Unusual Auricular T Wave in a Case of Myocardial Infarction, *AM. HEART J.* 31:501, 1946.
27. Roberts, J. T., and Loube, S. D.: The Congenitally Single Coronary Artery, *Anat. Rec.* 94:81, 1946.
28. Wartman, W. B.: Occlusion of the Coronary Arteries by Hemorrhage Into Their Walls, *AM. HEART J.* 15:459, 1938.
29. Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* 22:313, 1936.
30. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: Studies in the Pathology of Vascular Disease, *AM. HEART J.* 14:399, 1937.
31. Brown, J. W.: *Congenital Heart Disease*, London, 1939, John Bale Medical Publications, Ltd.
32. Soloff, L. A.: Anomalous Coronary Arteries Arising From the Pulmonary Artery, *AM. HEART J.* 24:118, 1942.
33. Hyrtl, J.: *Med. Jahrb. d. k. k. östern Staates*, 33:17, 1841.

A METHOD OF DETERMINING THE EFFECTIVE THERAPEUTIC LEVEL IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

A PRELIMINARY REPORT

J. G. SCHLICHTER, M.D.,* AND HELEN MACLEAN, A.B.

CHICAGO, ILL.

IN THE course of studies on the effective treatment of subacute bacterial endocarditis with penicillin over the past two years at this hospital, it was felt that there was need of some definite basis for determining adequate therapy for each specific infectious organism involved. A careful study of the literature demonstrated the universally empiric character of therapy and the lack of any objective criterion. The methods in general use all depend on indirect comparisons. The penicillin sensitivity of the organism is determined directly, but the blood level of penicillin during therapy is assayed by means of some "standard" organism. From these two measurements, continued therapy is planned so that a blood level as high or higher than the indicated sensitivity is maintained. This method has given, and is continuing to give, therapeutically satisfactory results in patients with highly sensitive organisms. In patients with more resistant organisms it has not been demonstrated that this is the proper approach.

It occurred to us that a more satisfactory method of outlining adequate therapy in cases with resistant organisms might be based on the action of a patient's own serum, during penicillin administration, upon the specific infectious organism isolated. As far as can be determined, such an approach to the problem has not been made. With this in mind, we have been selecting patients with comparatively resistant cases, in whom the organism has required 5 or more Oxford units of penicillin per cubic centimeter of culture medium to inhibit growth completely for eighteen hours, for closer study. Our findings seemed sufficiently promising to warrant this preliminary note.

After starting intensive therapy in the patients selected, adequate blood samples are drawn, preferably five minutes before the time of injection when the intermittent (intramuscular) method is employed, to permit making the usual

From the Cardiovascular and Bacteriology Departments, Research Institute, Michael Reese Hospital.

This study was supported by the Herbert G. Mayer Fund for Cardiovascular Research.

The Cardiovascular Department is supported in part by the Michael Reese Research Foundation.

Received for publication Oct. 18, 1946.

*Fellow of the Dazian Foundation.

TABLE I

PATIENT	ORGANISM FOUND	DATE	STANDARD TURBIDITY METHODS		GROWTH OF OWN ORGANISM IN OWN SERUM		RATIO OF SERUM PENICILLIN CONCENTRATION TO SENSITIVITY	
			SENSITIVITY OXFORD UNITS	SERUM LEVEL OXFORD UNITS PER C.C.	UN-DILUTED	DILUTIONS 1:2 1:4 1:8	UN-DILUTED	DILUTIONS 1:2 1:4 1:8
R. B.	<i>Streptococcus viridans</i>	10/24/46	5	10.24	+	+	2:1	
		11/11/46	5	10.24	±	+	2:1	
		11/27/46	5	40.96	0	+	8:1	4:1
		1/14/46	5	5.12*	+	+	1:1	2:1 1:1
H. W.	<i>Streptococcus viridans</i>	1/14/46	10	12.80	+	+	1.25:1	
		1/17/46	10	40.96	0	+	4:1	2:1 1:1
		1/19/46	10	25.60	+	+	2.5:1	1.25:1 0.6:1
		1/23/46	10	40.96	0	+	4:1	2:1 1:1

0, No growth; complete inhibition.
±, Good inhibition of growth but incomplete.
+, Growth; no effective inhibition.
*Prophylactic level for oral surgery, subsequent to treatment for subacute bacterial endocarditis.

serum level determinations in duplicate. The method is similar to that described by Rammelkamp* and others, and we employ routinely as our standard a strain of *Staphylococcus aureus*. The first set of tubes is inoculated in the usual manner with a 1:1000 dilution of a six-hour broth culture of this standard organism. The second set is similarly inoculated with a broth culture of the patient's own organism, diluted to give approximately the same number of organisms per cubic centimeter of diluent.

Typical findings in two cases are outlined in Table I. As shown, our results indicate that the serum level necessary to inhibit completely the growth of the patient's own organism in these cases was approximately the equivalent of four times the determined sensitivity of the organism. Serum dilutions having fewer Oxford units per cubic centimeter, even in ranges considerably above the actual sensitivity in vitro, showed graduated increases in the amount of growth (observed in stained smears), though the increase was never comparable to that of the control tube. Concurrent redeterminations of the sensitivity of the specific organism to penicillin in pure broth were occasionally made as a check and also to eliminate possible changes due to subculture on artificial media.

Patients with resistant organisms treated in this manner have achieved and maintained "clinical cures." Both patients on whom data are given in Table I became completely bacteria free under a therapeutic regimen based on the necessary levels of serum penicillin indicated by this test. Patient H. W. died of unrelated causes without a recurrence of the bacteremia. Patient H. B., who had subacute bacterial endocarditis, is of particular interest because he had been treated elsewhere on several occasions with the usual empiric type of therapy; on each occasion there was a relapse, with the reappearance of a *Streptococcus viridans* strain in blood cultures. With intensive therapy, which maintained levels for protracted periods of time sufficiently high to inhibit his own organism, a "clinical cure" was achieved, and he is back at work. He has remained free of any sign of infection for one year. At times, higher levels than necessary were reached, but complete inhibition of his strain of *Streptococcus viridans* was then obtained in all dilutions within the effective range.

As a result of these findings, we suggest that, in the treatment of resistant cases of bacterial endocarditis or acute septicemia with penicillin, therapy should be adequate to maintain, for a considerable period, serum levels sufficiently high to be completely bacteriostatic for the patient's own organism, as determined directly in vitro. This type of planned therapy will insure an optimal therapeutic level being reached in the blood stream.

*Rammelkamp, C. H.: Method for Determining Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**: 95, 1942.

COAGULATION OF THE BLOOD IN LUSTEROID TUBES: A STUDY OF NORMAL PERSONS AND PATIENTS WITH ARTERIAL OR VENOUS THROMBOSIS

ARNOLD H. KADISH, M.D.*
ROCHESTER, MINN.

THE introduction of anticoagulant therapy has created new interest in thrombosis and the relation of increased coagulability of the blood to the development of this condition. Unfortunately, however, the various tests developed for measuring the clotting time, while valuable in determining a prolongation, do not allow for accurate measurement of acceleration of the process. Indeed, ordinary determinations of coagulation time of whole blood usually give normal results. There would appear, therefore, great need for a test that would detect a shortening of the coagulation process. Because of this, a concerted effort has been made in recent years to develop such a procedure. The result is that several tests have been proposed. Each of these is, in its own way, time consuming and at best measures but one aspect of a complex reaction, often by the addition of heparin, thromboplastin, etc., substances with a not fully understood effect on the clotting process.

As a result it was felt worth while to study coagulation in vitro under conditions simulating as closely as possible coagulation in vivo; in other words, without the addition of substances concerned in coagulation.

To do this the coagulation time of blood in lusteroid (synthetic plastic resin surface) tubes was studied. These tubes were chosen because of the prolongation of coagulation time in them. Thus, with deceleration of the process, accurate measurement of significant decreases in coagulation time might be possible.

In this study, which includes a review of the pertinent literature on the subject, I have attempted (1) to establish normal values for the test, (2) to ascertain the reliability of the test, (3) to use the test in the study of arterial and venous thrombosis, and (4) to use the test in the study of patients receiving anticoagulant therapy. The first three points will be considered in this paper. The last will be taken up in a subsequent paper.



REVIEW OF LITERATURE

Tests Used for Detection of a Tendency to Thrombosis.—Chantemesse¹ in 1909 and Gelera² in 1921 devised a test of coagulation time based on the observation

*Fellow in Medicine, Mayo Foundation, Rochester, Minn.
Received for publication Oct. 24, 1946.

Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine.

that specimens of "good clot forming ability" require a higher concentration of anticoagulant solution in order to prevent coagulation as compared with specimens of "poor clot forming ability." In Chantemesse's test, a minute volume of blood was mixed with the same volume of solutions of potassium oxalate in increasing concentrations of from 1:1800 to 1:400. This series of mixtures of blood and oxalate was placed in capillary tubes. In one hour the tubes were inspected and the lowest concentration of oxalate which had prevented coagulation was noted. Since this minimal concentration in a normal case is a 1:800 solution of oxalate, a specimen of blood requiring a stronger solution for prevention of coagulation was considered to have better than normal coagulating ability.

More recently, de Takats and Gilbert^{3,4} made use of this principle in studying patients who had had arterial or venous thrombosis. Ten milligrams per cubic centimeter of heparin was injected intravenously and coagulation times were determined in capillary tubes at ten-minute intervals for forty minutes. They found the resistance to heparin marked (1) in the early postoperative period, (2) after cardiovascular accidents, and (3) in thromboangiitis obliterans. The blood of thirty-six patients showed heparin resistance in the immediate postoperative period for an average of four days; that of eighteen patients who had coronary thrombosis, cerebral thrombosis, arterial embolism and venous thrombosis, from whom samples of blood were taken within a few days after the occlusion, showed heparin resistance. In nine patients in whom blood was drawn weeks or months after the accident the response was normal. Six patients who had thromboangiitis obliterans were, without exception, classed as hyporeactors to heparin. De Takats^{3,4} further claimed that unless the disease was in the stage of complete remission, patients who had thromboangiitis obliterans might be expected to give such a response. Hyporeactors were defined as those patients whose capillary coagulation time ten minutes after the injection of heparin did not rise to more than 4.5 minutes and hyperreactors as those whose capillary coagulation time rose to more than 7.5 minutes in the same interval of time.

Waugh and Ruddick,^{5,6} by an *in vitro* technique involving use of increasing concentrations of heparin in a series of tubes to which 1 c.c. of blood to be studied was added, were able to construct curves by plotting units of heparin against coagulation time in minutes. These curves clearly illustrated an acceleration of the velocity of coagulation (1) during uncomplicated rest in bed, (2) after operation, (3) in acute inflammatory conditions, such as pneumonia, and (4) after severe hemorrhage. They also were able to demonstrate a slowing of coagulation during radium therapy for carcinoma of the cervix.

Hagedorn⁷ has devised an *in vitro* procedure which is simple, and he is of the opinion that it is reliable. It involves use of 0.5 c.c. of saline solution, 1 c.c. of blood, and 0.005 mg. of heparin. The normal range of coagulation time with his method is forty-five to eighty minutes.

Brambel and Loker,⁸⁻¹⁰ recognizing the need for the detection of the tendency to intravascular clotting before the appearance of thrombotic phenomena, proposed a test based on the prothrombin activity of serial dilutions of plasma. Essentially they modified Quick's method of determining prothrombin time by

using 12.5 per cent plasma. They stated that differences in clotting activity of the blood in normal and pathologic states cannot be demonstrated in undiluted plasma because of shortness of the clotting interval and limitations of experimental error. This is in agreement with Link,¹¹ who pointed out that prothrombin time of 12.5 per cent plasma will indicate the onset of hypoprothrombinemia before whole plasma will. The eightfold dilution prolongs the normal time. Using this method, Brambel found a significant shortening of the prothrombin time in thrombophlebitis, coronary thrombosis, and diabetic and frostbite gangrene. These observations were, in a way, compatible with the results of the heparin tolerance tests and indicated the action of substances other than thromboplastin and probably other than prothrombin alone. The advantages claimed for this test are that it can be carried out by a laboratory technician and that a reading can be ready in seconds instead of many minutes. De Takats,¹² however, has found that in his laboratory the end point of this procedure "is difficult to read and interpretation of the shorter than normal prothrombin times unclear."

Von Kaulla and Olivier¹³ and Müllly¹⁴ reported on the use of Lenggenhager's thrombin disintegration reaction in the detection of postoperative thrombosis. This reaction is based on the principle that the addition of defibrinated blood to recalcified citrated blood results in shortening of coagulation time to a value read in seconds. This value is similar to that which occurs on the addition of thromboplastin in the ordinary test of prothrombin time. They postulated that the shortening of the coagulation time in their test is due to the "thrombin" content of the defibrinated blood. They further showed that the use of blood thirty minutes after defibrination in this process resulted in a longer coagulation time than use of blood immediately after defibrination. This increase in coagulation time, they postulated, was due to antithrombin activity. Normal values for coagulation time were established as sixty seconds for thirty minutes after defibrination and 112 seconds for sixty minutes after defibrination. Von Kaulla and Olivier and others considered a postoperative coagulation time of less than forty seconds (thirty minutes after defibrination) as suggestive of a tendency to thrombosis. In thirty-three postoperative cases coagulation times of twenty to thirty seconds were obtained. They considered a coagulation time of less than seventy seconds (one hour after defibrination) as suggestive, and one of less than sixty seconds has been claimed as proof of thrombosis. The postoperative shortening of coagulation time as measured by this method they interpreted as being due to a postoperative decrease in the "antithrombin" content of blood.

✓ *Effect of Surface on Coagulation.*—A good many investigations have been carried out on the influence of external physical factors on coagulation. The problem of surface effect has been among the most significant of these since Freund,¹⁵ in 1886 demonstrated increased coagulation time for blood collected in vessels lined with petrolatum. Bordet and Gengou¹⁶ were of the opinion that the retardation of coagulation in oiled or paraffined test tubes as compared to that in untreated tubes was due to the fact that paraffin was not "wetable" by blood. Pickering and de Souza¹⁷ stated that clotting was due to lysis of a colloidal complex and that these surfaces (oil or paraffin) impeded such lysis. Gortner and

Briggs,¹⁸ using streaming measurement of electric potential (method involves forcing fluid through the pores of a diaphragm or capillary tube and measuring the potential set up across the diaphragm), showed that a bare glass capillary tube had a negative potential of approximately 30 millivolts. This potential was essentially zero (0) when the capillary tube was coated with paraffin. This substance would favor the absorption of positively charged colloids on the interface of the glass and blood serum. They postulated, then, that the initial step in blood clotting involves a surface concentration of some positively charged constituent and that the concentration is brought about by selective absorption.

Lampert^{19,20} and Neubauer and Lampert,²¹ using a method by which they could obtain a measurement of the surface tension of the blood in tubes of different materials, found definite relationship between coagulation time and surface tension of the blood in a particular container. As a result of this, Lambert began a search for test tubes of a material in which the relative surface tension of the blood would approach that in a paraffined test tube. This led him to the field of synthetic resins and he found a plastic synthetic surface similar to bakelite, called "athrombit," which he showed was superior to paraffin in its ability to delay coagulation. He constructed hematologic apparatus of athrombit, including a pipette for counting platelets, containers for direct transfusions of blood, special syringes. According to his technique the normal coagulation time for human blood at 37° C. is approximately thirty minutes in athrombit tubes.

Lampert's work also disclosed that various glass surfaces produced different effects on coagulation time; the poor glass which contained relatively much alkali produced a hastening of the process. This work resulted in the so-called Lampert's law; namely, that the anticoagulant power of a surface is inversely proportional to the force of adhesion exerted between that surface and water. The figures of Hirschboeck²² are of interest in this connection; he found that (1) force of adhesion of "lucite" or methyl methacrylate and water (capillary tube method) equals 0.038 Gm. per centimeter, (2) force of adhesion for paraffin and water equals 0.037 Gm. per centimeter, and (3) force of adhesion for glass and water equals 0.053 Gm. per centimeter. Hirschboeck²³ has shown, however, that, contrary to Lampert's law, coagulation time of normal human blood on a collodion surface is longer than on a paraffin surface even though the force of adhesion between blood and collodion is much greater than that between blood and paraffin.

Lozner and associates,²⁴ using normal platelet free human plasma (obtained through high speed centrifugation in lusteroid tubes) to which no anticoagulant was added, reported that the effect of glass surface "could not reasonably be attributed to lysis of platelets." Thus, by using 2 ml. of plasma they found the following average figures for coagulation time: (1) in glass, eleven minutes; (2) in collodion, sixty-four minutes; (3) in paraffin, forty-four minutes, and (4) in lusteroid, forty-nine minutes. By placing plasma rich in platelets (obtained by slow centrifugation in 2.5 per cent sodium citrate) in the four different tubes at room temperature for one hour, these workers found no significant change in platelet counts at the end of this period. Nevertheless, the coagulation time of plasma exposed to glass one hour prior to recalcification was markedly less than

that obtaining for the other three samples exposed for the same time to other surfaces. They then took 2 ml. samples of citrated platelet free plasma and found that on recalcification coagulation time in glass was normal, whereas those exposed to the other three surfaces had markedly prolonged coagulation times. Next, using normal citrated plasma rich in platelets prepared without exposure to glass and transferred to the four tubes, they found that the sample exposed to glass had much greater clot promoting power for hemophilic blood than did the other samples. Then this experiment was repeated with platelet free plasma and the same results were obtained. These investigators were able to note also that plasma placed first in glass vessels before transfer to one of the other surfaces behaved as plasma exposed to glass alone. They speculated that the so-called physiologic anticoagulant sought by many investigators as an explanation for the fluidity of blood may be found in the vascular endothelium which may resemble such surfaces as collodion, paraffin, and lusteroid in its behavior toward some noncellular plasma constituent as Gortner and Briggs, whose work has already been referred to, concluded.

Tocantins,²⁵ taking note of the longer plasma coagulation time in paraffin, collodion, lusteroid, and acryloid tubes than in glass, followed an interesting line of reasoning. He noted that normal plasma has the property of reducing the clot-accelerating action of the cephalin fraction of thromboplastic lipoprotein derived from homologous brain extracts and classified this as "anticephalin" activity. He showed that dilution of plasma (up to 20 per cent) or exposure to adsorbents decreased this anticephalin activity. He further found that either of these procedures, dilution up to 20 per cent, or absorption of plasma before placing it in the four tubes of varying surface, decreased the difference in coagulation time between that in glass and other vessels. He thus concluded that the extent of the difference in coagulation time between glass and the other surfaces was an approximate measurement of "anticephalin" activity.

Coagulation Time of Blood in Arterial or Venous Disease.—Shafiroff and co-workers,²⁶ using a modification of the Lee-White procedure for determining coagulation time, studied twenty-eight normal persons and found a slight tendency for blood from a lower extremity to clot faster than blood from an upper extremity. They further found this tendency exaggerated moderately among 156 patients who had varicose veins and exaggerated markedly in the blood of seven patients who had thrombophlebitis. Di Cio and Bay²⁷ reported a study of coagulation time by the Lee-White method in cases of intermittent claudication and gangrene of the legs. They divided their cases into four groups. In Group 1, which consisted of nineteen patients with intermittent claudication, coagulation time was short in ten patients (53 per cent) and normal in the remaining nine (47 per cent). Group 2 was made up of patients with intermittent claudication and essential hypertension; the coagulation time was short in twenty-two of thirty-two patients studied. Group 3 consisted of eighteen patients with gangrene of a lower extremity. In ten (55 per cent) coagulation time was decreased. Group 4 contained ten patients with gangrene of a lower extremity and arterial hypertension. In six (60 per cent) the coagulation time was shortened.

Theis and Freeland²⁸ studied the superficial venous and arterial blood in seven patients with acute thromboangiitis obliterans. They found (1) increased viscosity of blood, (2) rapid sedimentation rate, (3) rapid coagulation, (4) increased alkalinity, (5) low or normal cell counts, (6) low oxygen saturation of arterial blood, and (7) a low carbon dioxide content of the blood. They suggested that the anoxia could account for the hypercoagulability "just as rapid clotting in asphyxia is the result of deficient oxygen supply, according to Cannon and Mendenhall."²⁹

Davidson and MacDonald³⁰ found that after administration of dicumarol the coagulation time measured in lusteroid tubes, although more variable than when it was measured in glass, was much greater than that obtained in glass. The suggestion was made that the coagulation time in lusteroid tubes indicates the true coagulation defect more closely than does the coagulation time in glass. They noted no strict parallelism between coagulation time in lusteroid tubes (or glass) and concentration of prothrombin, and, furthermore, some of the patients had a moderately prolonged coagulation time in lusteroid without any profound lowering of prothrombin concentration. Similar studies which I carried out are to be reported in an ensuing paper.

PROCEDURE USED IN THIS STUDY

The following equipment was used: (1) a 5 c.c. syringe well lined with mineral oil and size 20 needle, lined with mineral oil; (2) tourniquet, (3) alcohol and sponge, (4) lusteroid tubes (12.5 mm. in diameter), and (5) Lee-White glass tubes (8 mm. in diameter).

The tourniquet was applied briefly above a large antecubital vein. The needle was inserted quickly into the vein with a minimum of trauma. If the vein was not punctured in the first attempt, the needle was withdrawn and another vein was used. The tourniquet was immediately removed and blood was withdrawn. The time at which the blood was first drawn into the syringe was noted. It was important that no bubbling or frothing occur within the syringe. If this occurred, the specimen of blood was discarded. Three cubic centimeters of blood were obtained; 2 c.c. were transferred to a lusteroid tube and 1 c.c. to a Lee-White glass tube. The tubes were tilted every thirty seconds. Coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot. It was important that the temperature be relatively constant. Throughout this work the tests were carried out at a room temperature of 24° to 26° C. Occasionally the tube was inverted without displacing the clot and yet the blood was liquid beneath the surface clot, as noted by free movement of a bubble within it. For these specimens the coagulation was considered complete the moment that the clot was firm throughout, as noted by the freezing of the bubble. The normal Lee-White coagulation time, according to this procedure, was considered to be 5 to 10 minutes, although many normal persons have a Lee-White coagulation time in the range of 4 to 12 minutes.

For cleaning tubes a soft brush was used. Tubes were rinsed thoroughly in hot water after cleaning with sodium lauryl sulfonate. They then were rinsed four times in distilled water and dried by inversion over night.

RESULTS OF TESTS

On Normal Persons.—The control group consisted of fifty subjects. Most of these were healthy, active adults, nurses, technicians, and physicians, and eighteen were ambulant patients who had conditions, such as duodenal ulcer, which would not affect the coagulation time of the blood. For purposes of this study these eighteen patients were considered normal and will be referred to in this way. Ages of these persons ranged from 18 to 40 years. There were twenty-seven men and twenty-three women. The results of the study of these normal subjects are shown in Table I. The coagulation time ranged from 14 to 28 minutes. The mean value was 19 minutes. The coagulation time of the blood of twenty-six subjects was 18 minutes or less and of twenty-four was 19 minutes or more.

TABLE I. NORMAL VALUES

COAGULATION TIME IN LUSTEROID TUBES (MIN.)	FREQUENCY
14	1
15	6
16	3
17	7
18	9
19	7
20	3
21	4
22	3
23	4
25	2
28	1
Total	50

Tests of the coagulation time of the blood of five normal persons were made in new lusteroid tubes and these results were compared with those obtained for five normal subjects when the test was made in lusteroid tubes of the original batch which had been washed one or more times. The results are shown in Table II. Although the sample is small, it is apparent that slightly longer

TABLE II. COMPARISON OF RESULTS OBTAINED IN NEW AND OLD LUSTEROID TUBES

NEW TUBES		OLD TUBES	
TUBE	COAGULATION TIME (MIN.)	TUBE	COAGULATION TIME (MIN.)
1	22	1	23
2	18	2	20
3	18	3	19
4	28	4	20
5	25	5	18
Mean	22.2	Mean	20.0

coagulation times and a slightly longer mean occurred when new tubes were used. This increase is, however, within the range of experimental error of the test (Table III).

To ascertain further the reliability of the lusteroid procedure as outlined previously, it was decided to study coagulation time in each of ten tubes, using a part of the same sample of blood in each tube. For this purpose 20 c.c. of blood were drawn from each of two normal young adults and 2 c.c. were placed in each tube. There was a maximal variation of 2.5 minutes (Table III), exclusive of any consideration of variation due to blood first leaving vein as against that most recently leaving the vein in the 20 c.c. samples used.

TABLE III. RELIABILITY OF TEST USING NORMAL SUBJECTS

CASE 1		CASE 2	
LUSTEROID TUBE	COAGULATION TIME (MIN.)	LUSTEROID TUBE	COAGULATION TIME (MIN.)
1	17.5	1	23.0
2	17.5	2	22.0
3	20.0	3	22.0
4	18.0	4	21.5
5	18.0	5	22.0
6	18.0	6	23.0
7	18.0	7	23.0
8	19.0	8	22.5
9	18.5	9	22.5
10	18.0	10	23.0
Maximal variation:	2.5		1.5

Several months after this investigation was begun a new batch of lusteroid tubes arrived. Their appearance was different from the first batch with which all our results were obtained. The second batch of tubes gave consistently lower coagulation times than did the original, with a range of 6 to 13 minutes under the conditions outlined previously. It was decided, therefore, not to use these tubes in this experiment. This suggests that the normal coagulation time in lusteroid tubes must be obtained for the tubes in use, as was done with the tubes in this study, before any investigation is undertaken. This probably accounts for the great variation of the normal values reported in the literature. A similar variation for glass has been reported by Lampert¹⁹ and is referred to elsewhere in this paper.

In Cases of Arterial and Venous Thrombosis.—The coagulation time of the blood of eighteen patients who had arteriosclerosis obliterans was determined in lusteroid tubes. The results are given in Table IV.

The coagulation time in nine patients (50 per cent) was less than normal by lusteroid method and in four by the Lee-White method (22 per cent). In Cases 3, 4, and 5 acute arterial occlusion had occurred two to three weeks previously. In Case 16 the acute occlusion had occurred ten days before the test;

TABLE IV. ARTERIOSCLEROSIS OBLITERANS

CASE	AGE (YR.) AND SEX	COAGULATION TIME	
		LEE-WHITE (MIN.)	LUSTEROID (MIN.)
3	50 M	7.5	13.0
4	65 M	5.0	18.0
5	63 M	5.0	11.0
6*	60 M	4.0	10.0
7	61 M	6.0	14.0
8	66 M	6.0	12.0
9*	65 M	4.0	10.0
10	50 M	7.0	37.0
11	65 M	5.0	14.0
12*	47 M	4.0	13.0
13	64 F	6.0	11.5
14	76 M	10.0	28.0
15	71 M	9.0	19.0
16	67 F	4.5	6.0
17	65 F	9.0	14.0
18	63 M	6.0	11.0
19	67 M	6.0	23.0
20	61 F	7.0	21.0

*Diabetic patient.

this patient was the one in whom occlusion was the most recent. Marked hyperlipemia was present in but one patient (Case 10) at the time of this study. The relation of this condition to the coagulation time in the lusteroid tube of 37 minutes is conjectural.

The coagulation time of the blood in lusteroid tubes was determined in ten patients with thromboangiitis obliterans. The results are given in Table V. In only three of the ten (30 per cent) was the coagulation time as determined in lusteroid tubes less than the normal. By the Lee-White method it was within limits of normal in all patients. In the six patients in whom the disease was

TABLE V. THROMBOANGIITIS OBLITERANS

CASE	SMOKED	AGE (YR.)	COAGULATION TIME		CLINICAL ACTIVITY
			LEE-WHITE (MIN.)	LUSTEROID (MIN.)	
21	Yes	40	6.0	5.0	Active; infected ulcer of toe
22	No	59	5.0	15.0	Inactive
23	No	36	6.5	20.0	Inactive
24	No	39	5.0	23.0	Active with recurrent superficial phlebitis
25	No	42	7.0	14.0	Active; no phlebitis
26	No	37	10.0	25.0	Active with mild migratory phlebitis
27	No	45	8.0	19.0	Arrested
28	No	36	5.0	12.0	Arrested
29	No	36	10.0	13.0	Active; no phlebitis
30	No		6.0	15.0	Active with phlebitis

clinically active, the coagulation time measured in the lusteroid tubes was decreased in only two. In one patient (Case 21), two weeks after cessation of smoking, the lusteroid coagulation time was 10.5 minutes and the Lee-White coagulation time remained unchanged.

The coagulation time of the blood in lusteroid tubes was determined in eleven patients with thrombophlebitis. The results are given in Table VI. In eight of nine patients with acute thrombophlebitis, the coagulation time in the lusteroid tubes was less than normal. Normal coagulation times were found in the two patients (Cases 33 and 36) in whom the phlebitis was subsiding. In one patient (Case 38) with arteriosclerosis obliterans in whom phlebitis of the calf developed while the patient was under treatment for the arterial disease, the lusteroid coagulation time changed from 14 to 7 minutes, but the Lee-White coagulation time remained unchanged at 6 minutes.

TABLE VI. THROMBOPHLEBITIS (EXCLUDING THAT ASSOCIATED WITH THROMBOANGIITIS OBLITERANS)

CASE	PHLEBITIS		COAGULATION TIME	
	TYPE	SITE	LEE-WHITE (MIN.)	LUSTEROID (MIN.)
31	Acute	Iliofemoral	5.0	10.5
32	Acute	Iliofemoral	6.0	8.5
33	Subacute, subsiding eight days after onset	Deep calf	8.0	22.0
34	Acute, hours	Great saphenous	6.0	8.0
35	Acute	Deep calf	5.0	5.5
36	Subsiding	Great saphenous	7.0	19.0
37	Acute	Deep calf	8.0	18.0
38	Acute	Deep calf	6.0	7.0
39	Acute	Iliofemoral	4.5	4.0
40	Acute	Deep calf	5.0	5.0
41	Acute	Great saphenous	6.0	9.0

The reliability of the test in a case in which the coagulation time was decreased is shown in Table VII. The same procedure as that used to determine the reliability of the test on normal subjects was employed (Table III). The blood in this study was from a patient who had thrombophlebitis (Case 35, Table VI).

The variation in coagulation time was never greater than thirty seconds; that is, no greater difference than the time it took to invert the tube once.

Influence of Diameter of the Tube.—Inasmuch as the lusteroid tube has a greater internal diameter than the Lee-White tube, it was important to note how much of the prolongation of coagulation time in the former tube was due merely to greater diameter. To study this, a lusteroid tube and a glass tube of approximately the same size (12 mm. in diameter) as the lusteroid tube (12.5 mm. in diameter) were used. Simultaneous coagulation times were determined with a

TABLE VII. THROMBOPHLEBITIS OF DEEP CALF VEINS (CASE 35)

TUBE	COAGULATION TIME, IN LUSTEROID TUBES (MIN.)
1	6.0
2	5.5
3	6.0
4	5.5
5	5.5
6	6.0
7	6.0
8	6.0
9	5.5
10	6.0

part of the same blood sample in each of these tubes. The Lee-White coagulation time is listed merely for sake of completeness. The results are shown in Table VIII.

A study of the coagulation times in the glass and lusteroid tubes shows that the effect of the lusteroid tube is largely a matter of quality of surface, since this is the only significant variable that could influence the coagulation times in the 12 mm. glass tube and the lusteroid tubes.

TABLE VIII. COAGULATION TIMES IN LEE-WHITE GLASS AND LUSTEROID TUBES

TYPE OF CASE	COAGULATION TIME (MIN.)		
	LEE-WHITE TUBE*	GLASS TUBE (LARGE)†	LUSTEROID TUBE‡
Arteriosclerosis obliterans; femoral occlusion three weeks previously	5	7.5	13.0
Arteriosclerosis obliterans; iliac occlusion two weeks previously	5	11.0	18.0
Arteriosclerosis obliterans; two weeks after acute femoral occlusion	5	6.0	11.0
Arteriosclerosis obliterans	6	10.0	14.0
Acute iliofemoral thrombophlebitis	5	5.0	10.5
Recurrent cerebral thrombosis	6	12.0	12.0
"Burned out" thromboangiitis obliterans	5	10.0	15.0
Diabetes; arteriosclerosis obliterans	4	5.0	10.0
Arteriosclerosis obliterans	7	8.0	21.0
Arteriosclerosis obliterans	4	6.0	21.0

*Eight millimeters in diameter containing 1 c.c. of blood.

†Twelve millimeters in diameter containing 2 c.c. of blood.

‡Twelve and one-half millimeters in diameter containing 2 c.c. of blood.

SUMMARY

Coagulation times in the lusteroid tubes used throughout this work were in the range of 14 to 28 minutes in a series of fifty normal controls. There is apparently no significant variation in coagulation time obtained when new or used

tubes from the same batch were used. However, normal values must be determined for each new batch of tubes before they are put into use.

The reliability of the test varies with the range of coagulation time. In the short range the experimental variation is very small; in the normal range it is somewhat greater.

In nine (50 per cent) of the eighteen patients with arteriosclerosis obliterans studied, the coagulation times as measured by the lusteroid method were definitely less than for the normal subjects. No cases of acute occlusion were studied.

Ten patients with clinically active or quiescent thromboangiitis obliterans with and without phlebitis were studied. In only three (30 per cent) was there any significant decrease of lusteroid coagulation time. These were two of the group of five patients with clinically active cases.

The most pronounced shortening to less than normal of lusteroid coagulation time occurred in the patients with acute thrombophlebitis. It was noted in eight of the nine patients studied. Normal coagulation times were found in the two patients with subsiding thrombophlebitis. It is suggested that determination of the coagulation time in lusteroid tubes may be of value in indicating a tendency to thrombosis.

REFERENCES

1. Chantemesse: Quoted by Cohen, M. S.: The Coagulation-time of the Blood as Affected by Various Conditions, *Arch. Int. Med.* 8:684, 820, 1911.
2. Gelera: Quoted by Nygaard, K. K.: Hemorrhagic Diseases; Photo-electric Study of Blood Coagulability, St. Louis, 1941, The C. V. Mosby Co., chap. 1, p. 28.
3. de Takats, Geza: Heparin Tolerance; A Test of Clotting Mechanism, *Surg., Gynec. & Obst.* 77:31, 1943.
4. de Takats, Geza, and Gilbert, N. C.: The Response to Heparin: a Test of the Clotting Mechanism, *J.A.M.A.* 121:1246, 1943.
5. Waugh, T. R., and Ruddick, D. W.: Test for Increased Coagulability of Blood, *Canad. M. A. J.* 50:547, 1944.
6. Waugh, T. R., and Ruddick, D. W.: Studies on Increased Coagulability of the Blood, *Canad. M. A. J.* 51:11, 1944.
7. Hagedorn, A. B.: Personal communication to the author.
8. Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, *Proc. Soc. Exper. Biol. & Med.* 53:218, 1943.
9. Brambel, C. E., and Loker, F. F.: Application of Dicumarin (3,3'-Methylene-bis-[4-Hydroxycoumarin]) in Trauma and Gangrene, *Arch. Surg.* 48:1, 1944.
10. Brambel, C. E.: Thromboplastic Reagent; Development of a More Suitable Preparation for Measuring Accelerated Clotting Tendency and for Use Following Administration of Dicumarin (3,3'-Methylene-bis-[4-Hydroxycoumarin]), *Arch. Surg.* 50:137, 1945.
11. Link, K. P.: The Anticoagulant From Spoiled Sweet Clover Hay, *Harvey Lect.* 39:162-216, 1944.
12. de Takats, Geza: Thromboembolism, *Minnesota Med.* 28:843, 1945.
13. von Kaulla, K. N., and Olivier, Willi: Beitrag zur Thrombinabbaureaktion, *Deutsche Ztschr. f. Chir.* 256: 422, 1942.
14. Müllly, M.: Zur Thrombinabbaureaktion nach Lenggenhager, *Monatschr. f. Geburtsh. u. Gynäk.* 116: 174, 1943.
15. Freund: Quoted by Bordet and Gengou.¹⁶
16. Bordet, Jules, and Gengou, Octave: Recherches sur la coagulation du sang, *Ann. Inst. Pasteur.* 17:822, 1903.
17. Pickering, J. W., and de Souza, D. H.: The Fluidity and Coagulation of the Blood, *Biochem. J.* 17:747, 1923.
18. Gortner, R. A., and Briggs, D. R.: Glass Surfaces Versus Paraffin Surfaces in Blood-clotting Phenomena—a Hypothesis, *Proc. Soc. Exper. Biol. & Med.* 25:820, 1928.

19. Lampert, Heinrich: Die physikalische Seite des Blutgerinnungsproblems und ihre praktische Bedeutung, Leipzig, 1931, Georg Thieme, p. 127.
20. Lampert, Heinrich: Die Bestimmung der Blutgerinnungszeit, München. med. Wchnschr. 77:586, 1930.
21. Neubauer, Otto, and Lampert, Heinrich: Ein neuer Bluttransfusionsapparat. Zugleich ein Beitrag zur Kenntnis der thrombogenen Eigenschaften fester Stoffe, München. med. Wchnschr. 77:582, 1930.
22. Hirschboeck, J. S.: Delayed Blood Coagulation in Methyl Methacrylate (Boilable "Lucite") Vessels, Proc. Soc. Exper. Biol. & Med. 47:311, 1941.
23. Hirschboeck, J. S.: Delayed Blood Coagulation and Absence of Clot Retraction in Collodion Lined Vessels, Proc. Soc. Exper. Biol. & Med. 45:122, 1940.
24. Lozner, E. L., Taylor, F. H. L., and MacDonald, Harriet: The Effect of Foreign Surfaces on Blood Coagulation, J. Clin. Investigation 21:241, 1942.
25. Tocantins, L. M.: Influence of Contacting Surface on Coagulability and Anticephalin Activity of Normal and Hemophilic Plasmas, Am. J. Physiol. 143:67, 1945.
26. Shafiroff, B. G. P., Doubilet, H., Barcham, I. S., and Co Tui: The Coagulability of Venous Blood of Normal and Diseased Legs; a Study of 191 Subjects, Ann. Surg. 118:482, 1943.
27. di Cio, A. V., and Bay, R.: Coagulación de la sangre en las Claudicaciones intermitentes y gangrenas de las extremidades inferiores, Prensa méd. argent. 30:789, 1943.
28. Theis, F. V., and Freeland, M. R.: The Blood in Thromboangiitis Obliterans, Arch. Surg. 38:191, 1939.
29. Cannon, W. B., and Mendenhall, W. L.: Factors Affecting the Coagulation Time of Blood. III. The Hastening of Coagulation by Stimulating the Splanchnic Nerves, Am. J. Physiol. 34:243, 1914; IV. The Hastening of Coagulation in Pain and Emotional Excitement, Am. J. Physiol. 34:251, 1914.
30. Davidson, C. S., and MacDonald, Harriet: A Critical Study of the Action of 3-3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. 205:24, 1943.

COAGULATION TIME OF THE BLOOD IN LUSTEROID TUBES: A STUDY OF PATIENTS RECEIVING DICUMAROL

ARNOLD H. KADISH, M.D.*
ROCHESTER, MINN.

THE coagulation time in Lee-White and lusteroid tubes was determined daily in six patients who had received dicumarol for at least two weeks. The method used has been described in a previous paper but will be mentioned briefly here.

A tourniquet was applied above the antecubital vein and the needle was inserted into the vein. The tourniquet was removed and 3 c.c. of blood were withdrawn into the oiled syringe without bubbling or frothing. The time when the blood entered the syringe was noted. Two cubic centimeters of blood were transferred to a lusteroid tube and 1 c.c. to a Lee-White glass tube. The tubes were tilted every thirty seconds and coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot; if the blood were liquid underneath a clot, however, coagulation was assumed to be complete as soon as the bubble was frozen in place. Tests were made at a room temperature of 24° to 26°C.

Prothrombin times were obtained simultaneously by a modification of the Quick method.

Findings typical of the group investigated are presented graphically in Figs. 1 and 2. The data in Fig. 1 were obtained in the case of a man 62 years of age who had arteriosclerosis obliterans and had suffered from acute occlusion of the iliac artery two weeks before admission. The initial coagulation time in a lusteroid tube was 18 minutes. Coagulation times and prothrombin times were determined daily for a period of fifteen days while the patient was receiving dicumarol.

As in all the cases studied, the coagulation time of blood determined in lusteroid tubes was delayed more than that determined in the Lee-White tubes after administration of dicumarol. The tendency for the coagulation time measured in lusteroid tubes to increase the longer the patient had received dicumarol, despite the fact that the concentration of prothrombin was maintained at a relatively constant level as indicated by the prothrombin time test, is evident. This is at least suggestive that dicumarol may affect the clotting mechanism in more ways than one.

Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the degree of M. S. in Medicine.

Received for publication Oct. 24, 1946.

*Fellow in Medicine, Mayo Foundation.

The data in Fig. 2 were obtained in the case of a man 50 years of age who had hypertensive and arteriosclerotic heart disease. While in the hospital under treatment for this condition he suffered from an acute pulmonary embolism. The coagulation time had not been determined in lusteroid tubes prior to the embolism. It was determined ten minutes and several hours after embolism.

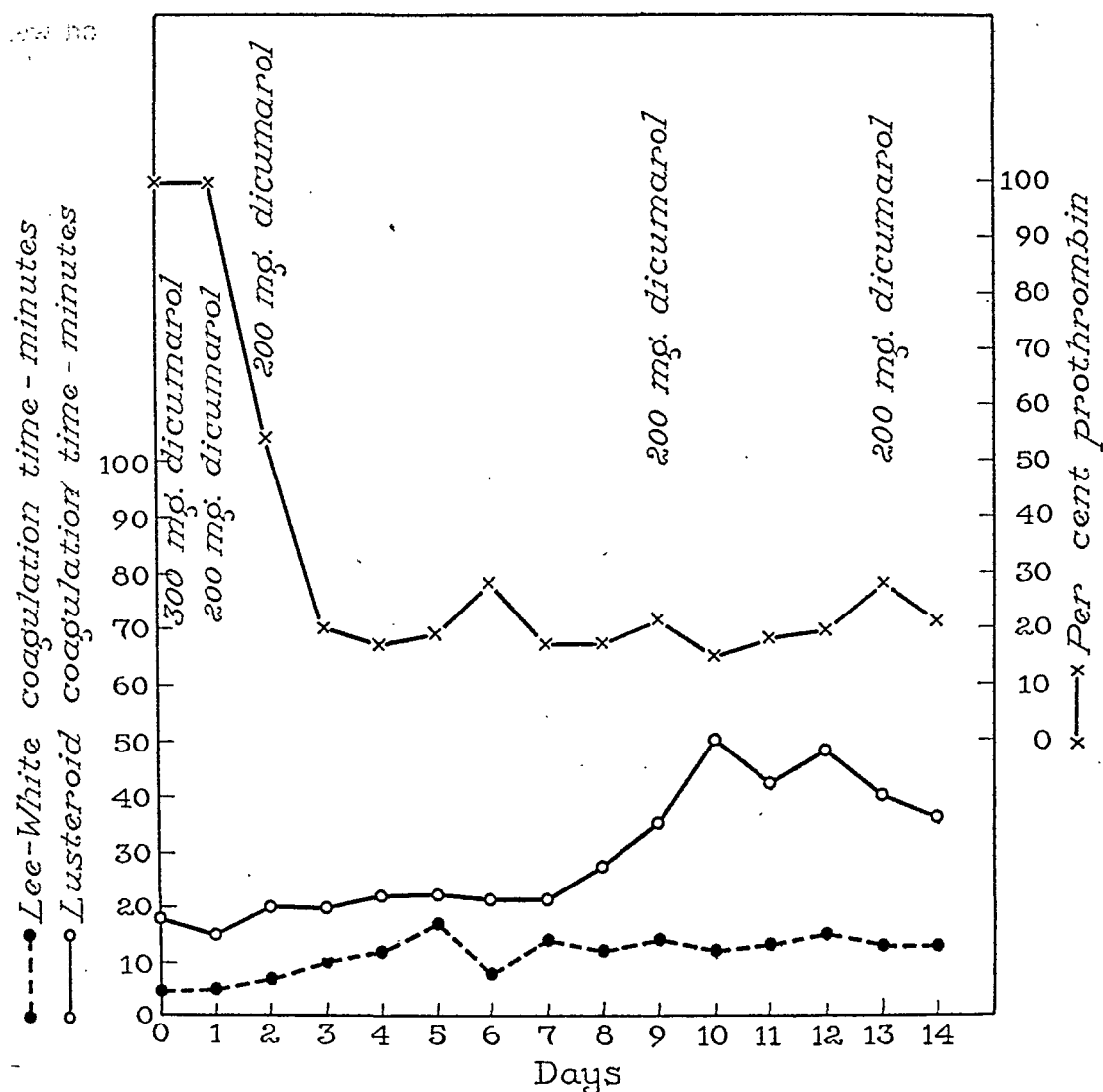


Fig. 1.—Coagulation time and percentage of prothrombin of the blood of a patient who had arteriosclerosis obliterans and was receiving dicumarol because of acute occlusion of the iliac artery.

The patient remained in the hospital an additional two weeks during which period he was given dicumarol. In this case, as in all cases studied, it was evident that there was no strict parallelism between coagulation times determined in lusteroid or Lee-White tubes and the concentration of prothrombin. However, the lusteroid test appears to be more sensitive to changes in coagulation following administration of dicumarol than the Lee-White procedure. An interesting observation is the decrease in lusteroid coagulation time to a value of 14 minutes on the twelfth day (Fig. 2). This was associated with return of pain in the thorax. The pain occurred despite the fact that the concentration of prothrombin on that

day was in the full therapeutic range. The clinical course was suggestive of the possibility of recurrence of embolism.

Coagulation times were determined simultaneously with part of the same sample of blood, using glass and lusteroid tubes of the same size (Table I) in order to test whether the diameter of the tube had any effect on the coagulation time. For these tests 5 c.c. of blood were drawn each time.

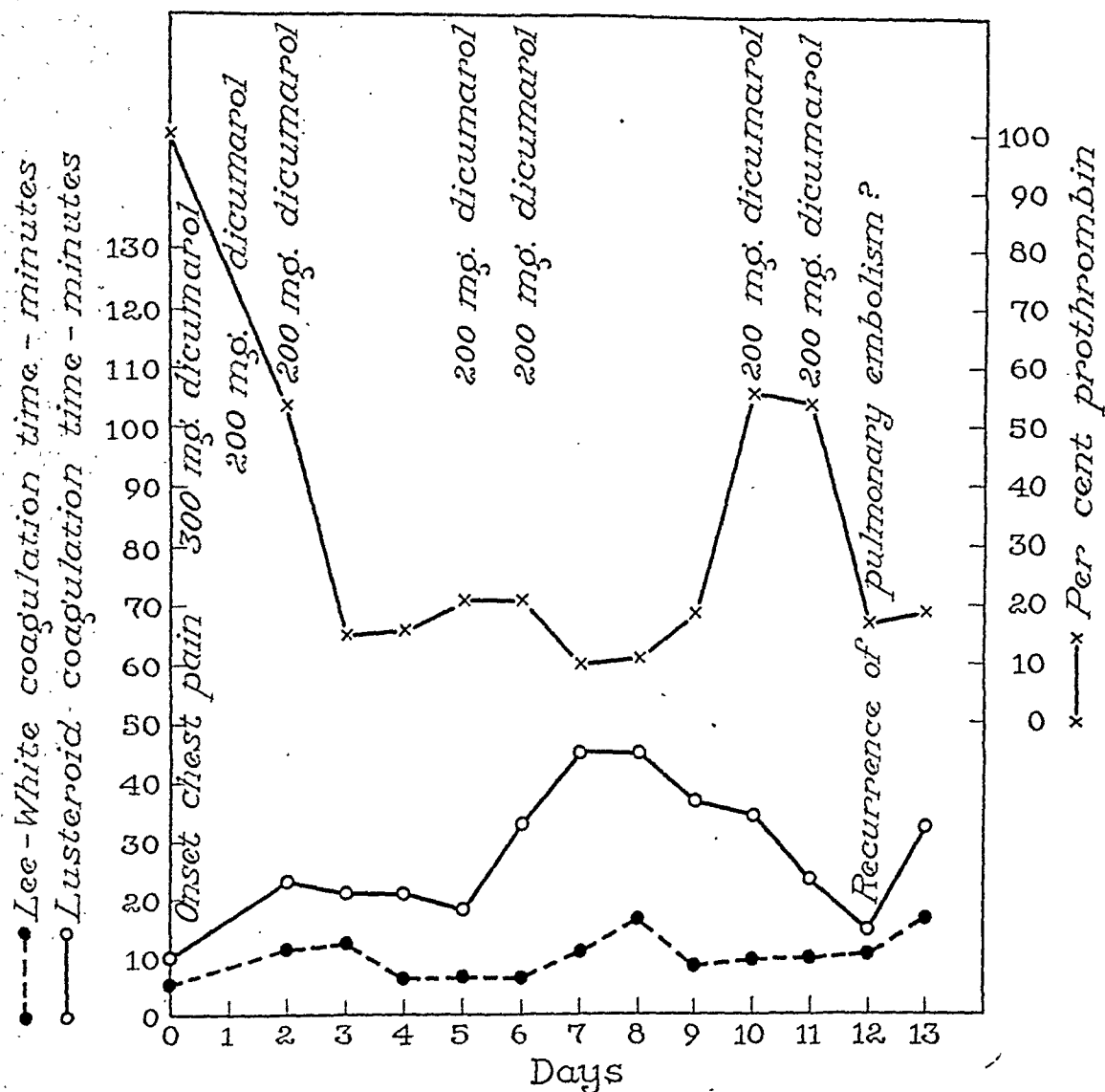


Fig. 2. — Coagulation time and percentage of prothrombin in the blood of a patient who had had an acute pulmonary embolism. Patient was being treated with dicumarol.

The effect of the lusteroid tube was shown to be largely a matter of quality of surface, as this was the only significant variable in the coagulation times determined in large glass and lusteroid tubes in these cases. This corresponds with observations made in a previous paper.

The reliability of the lusteroid test of coagulation time under the condition of prolongation of coagulation time is shown in Table II. For this test 20 c.c. of blood were drawn from a patient who was receiving dicumarol because of acute phlebitis of the leg. Two cubic centimeters of this blood were placed in each of the ten lusteroid tubes. The concentration of prothrombin was 20 per

TABLE I. PATIENTS RECEIVING DICUMAROL

CASE	DOSE OF DICUMAROL, MG.	COAGULATION TIME, MINUTES		
		LEE-WHITE TUBE*	LARGE GLASS TUBE†	LUSTEROID TUBE‡
1	Controls§	5.0	11.0	18.0
	300	4.0	10.0	17.0
	200	7.0	8.0	20.0
	200	10.0	14.0	20.0
		12.0	10.0	22.0
		17.0	13.0	21.5
		8.0	11.0	21.0
		14.0	14.0	21.0
		12.0	14.0	27.0
	200	14.0	23.0	35.0
		12.0	17.0	50.0
		13.0	14.0	42.0
2	Controls§	5.5	7.5	12.0
	300			
	200	8.0	10.0	16.0
	200	5.5	9.5	17.0
		4.0	12.0	17.0
		6.0	8.0	17.0
		9.0	19.0	21.0
		8.0	15.0	21.0
		11.0	13.0	16.0
		10.0	15.0	21.0
3	Controls§	5.0	6.0	11.0
	300	6.5	8.5	20.0
	200	14.0	12.0	19.0
		18.0	17.0	24.0
		6.0	11.0	17.0
	200	7.0	10.0	20.5
	200	7.0	11.0	19.0
		14.0	16.0	32.0
		12.0	13.0	26.0
		15.0	23.0	35.0

* 8 mm. in diameter containing 1 c.c. of blood.

†12 mm. in diameter containing 2 c.c. of blood.

‡12.5 mm. in diameter containing 2 c.c. of blood.

§Before administration of dicumarol.

TABLE II. RELIABILITY OF TEST IN PATIENT RECEIVING DICUMAROL

TUBE	COAGULATION TIME IN LUSTEROID TUBES, MINUTES
1	28
2	29
3	32
4	33
5	31
6	31
7	31
8	31
9	29
10	30

cent in this sample. Evidence in Table II and in previous work suggests that the test is less reliable, that is, subject to greater variation for patients receiving dicumarol than for normal persons or patients who have a tendency to thrombosis but have not been treated with dicumarol.

COMMENT

These studies of the coagulation time in lusteroid and glass tubes of patients receiving dicumarol largely confirm the previous work of Davidson and MacDonald.* I found that the coagulation time of the blood of these patients was variable and more so when it was determined in lusteroid tubes than in glass. There was no strict parallelism between coagulation time determined in lusteroid or glass tubes and the concentration of prothrombin, and furthermore, some of the patients had prolongation of coagulation time in lusteroid tubes without any pronounced lowering of the concentration of prothrombin. That this might be due to the fact that I did not use diluted plasma in the determination of prothrombin is a matter of conjecture. It has been suggested by others that dicumarol affects fibrinogen, causing a depletion of this substance. So far, however, this work is only suggestive, as no good direct test for determining concentration of fibrinogen has been devised. Throughout the study it was evident that after administration of dicumarol the coagulation time of blood determined in lusteroid tubes showed much greater delay than that determined in glass tubes. There was also a tendency for the coagulation time determined in lusteroid tubes to become longer as the time that the patient received the drug increased despite the fact that the concentration of prothrombin was maintained at a relatively constant level as indicated by the test of prothrombin time.

*Davidson, C. S., and MacDonald, Harriet: A Critical Study of the Action of 3-3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), *Am. J. M. Sc.* **205**:24, 1943.

AN ELECTROCARDIOGRAPHIC STUDY OF ONE HUNDRED FOURTEEN CONSECUTIVE CASES OF TRICHINOSIS

MAJOR SYLVAN D. SOLARZ*

MEDICAL CORPS, ARMY OF THE UNITED STATES

THERE have been occasional reports of electrocardiographic changes occurring during the course of trichinosis; for the most part only small numbers of cases have been available for study.¹⁻⁴ It has been shown beyond doubt that there is actual invasion of the myocardium by the parasites with a definite, although nonspecific, myocarditis resulting. The pathology has been adequately reviewed by Saphir⁵ and by Spink.² The electrocardiographic changes are usually transitory, and in the majority of patients the records return to normal. An explanation for this may be found in the study of the pathogenesis of the myocarditis. Dunlap and Weller,⁶ working with mice, have shown that although larvae are present in the cardiac muscle early in the disease, no encystment takes place in the myocardium by the time it occurs in the skeletal musculature. They believe that some factor in the heart muscle prevents encystment and that the myocarditis is due to the active migration of the larvae rather than to a blood-borne substance.

Because of the evidence of a definite anatomic process taking place in the myocardium during the disease it may be assumed that the electrocardiographic changes are due to this process rather than to any theoretical toxin or reflex action.

An epidemic of trichinosis broke out on the post at which this general hospital is located and one hundred eighteen patients with this disease were admitted to the hospital. A detailed clinical study of the epidemic is in preparation.⁷

All of the patients were admitted during the acute, invasive phase of the disease. Nearly all showed marked periocular edema and subconjunctival hemorrhages, and complained of muscle pains. There were no fatalities.

Initial electrocardiograms were obtained from 112 patients within three days of admission. All tracings were recorded in the supine position, and the standard limb leads with the addition of CF₂ and CF₄ were taken. Abnormal and borderline records were repeated at approximately weekly intervals until they had returned to normal or until it was not possible to get further records because of the patient's transfer to another installation. Additional electrocardiograms were obtained at random from patients whose initial tracings had

From the Cardiovascular Section, Wakeman General Hospital, Camp Atterbury, Ind.
Received for publication Nov. 1, 1946.

*Now at the Michael Reese Hospital, Chicago, Ill.

been normal. This was done in an effort to determine whether or not any changes might occur later in the course of the disease after the actual invasive period was over. Such changes were not found. A total of 255 separate electrocardiograms from the epidemic were available for study. In addition to these records two previous patients are included in the series. These were the only other cases of trichinosis that had been recognized in this hospital.

None of the 114 patients had any signs or symptoms referable to the cardiovascular system. Because of the exigencies of the military situation that prevailed at the time of the outbreak of the epidemic, a complete cardiovascular study could not be made on every patient. However, all patients had a careful physical examination, including blood pressure readings, and were seen daily. All patients whose findings aroused suspicion of clinical cardiovascular disease were referred to the author for further investigation. There were, however, no patients in whom a purely clinical diagnosis of myocarditis was justified.

The criteria for abnormality of the various electrocardiographic complexes were those agreed upon in the standard texts and by the American Heart Association.⁸ Several patients who showed RS-T or T-wave variations in Leads I and II when their heart rates were rapid, were restudied on the same day, one hour after administration of 0.2 Gm. of pentobarbital sodium. This was done because it has been observed that in some individuals these changes might be caused by fear or new emotional situations. There were six patients in this group, and all of their records became normal after sedation. Therefore, they are not included in the abnormal group.

FINDINGS

Definitely abnormal electrocardiograms were found in twenty-four of the 114 patients studied (21 per cent). The various abnormalities are listed for each patient in Table I.

P-R Interval.—There were two patients (8.2 per cent) with prolongation of the P-R interval (Table I). In one patient (Case 58, Fig. 1) this was the only definite abnormality, although the QRS voltage was just below the lower limit of normal. The P-R interval was 0.27 second on admission and gradually fell to normal in seven weeks; at the same time the QRS voltage increased. In the other instance (Case 14, Fig. 2), the P-R interval was 0.22 second on admission, increased to 0.24 second on the sixth day, and then returned to normal by the eighteenth day. Associated abnormalities are discussed below and may be ascertained from the illustration.

QRS Duration.—This was prolonged to 0.12 second in seven patients (29.2 per cent), but there were no associated abnormalities in any of the electrocardiograms. All of these patients were followed until their transfer from the hospital three months after admission, and at that time there had been no change in the tracings (Fig. 3).

It might be argued that the QRS duration in these patients was normally 0.12 second, and, consequently, that these records do not represent abnormalities

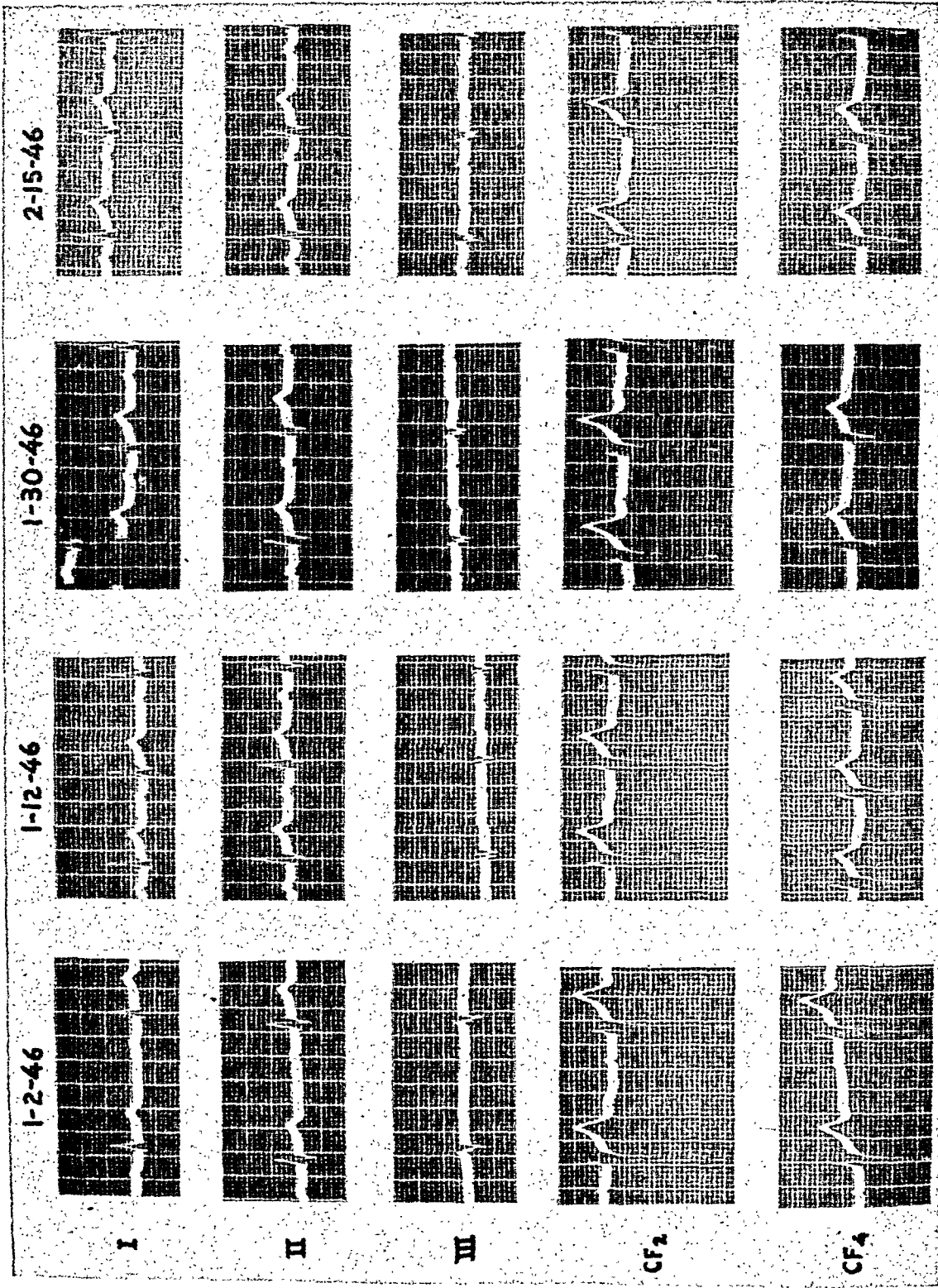


Fig. 1.—Case 58. The P-R interval is prolonged, and the voltage is borderline normal on Jan. 2, 1946. Note the increase in amplitude of the T wave in Lead I although it was never abnormally small. Discussed in text.

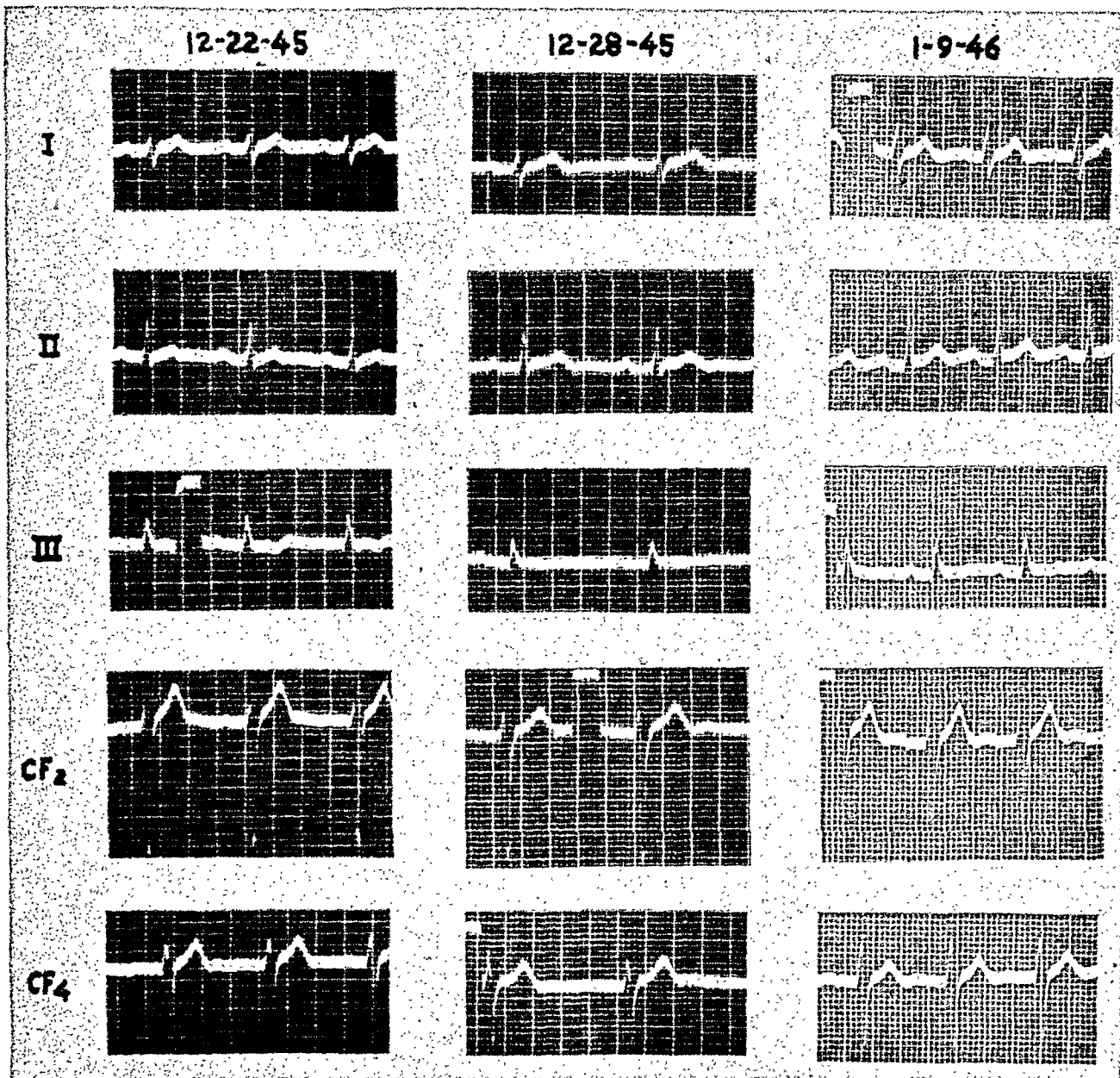


Fig. 2.—Case 14. Prolonged P-R interval increasing in six days and then reverting to normal. There is low voltage of the QRS and a flattened T wave in Lead II. Note the increase in amplitude of the T wave in Lead I. Discussed in text.

which might be attributed to trichinosis. In a survey of 1,000 healthy young aviators in an age group comparable to the present series, Graybiel and co-workers⁹ found only eight cases (0.8 per cent) in whom the QRS measured 0.12 second. Ferguson and O'Connell¹⁰ found an incidence of 0.11 per cent among 1,812 young men. Shipley and Halloran¹¹ found a similar QRS duration in 0.5 per cent of 200 cases, while Hall, Stewart, and Manning¹² found only two instances in which the QRS duration was longer than 0.10 second among 2,000 air force personnel. Graybiel and co-workers⁹ conclude that "QRS complexes of 0.12 second duration, even when observed in the electrocardiograms from young, apparently healthy persons, are usually caused by some abnormality, but in rare instances may not have any pathological significance."

TABLE I. ABNORMALITIES WHICH OCCURRED IN EACH OF ABNORMAL ELECTROCARDIOGRAMS IN THE SERIES; CASE 14 HAD AN INITIAL P-R OF 0.22 SECOND ON ADMISSION, AND THIS INCREASED TO 0.24 SECOND ON THE SIXTH DAY

CASE	P-R INTERVAL	QRS VOLTAGE	QRS DURATION	RS-T SEGMENT AND T WAVE	RECOVERY	REMARKS
1	Normal	Normal	Normal	T flattened in Lead II	1 week	T normal in Lead I but amplitude increased
2	Normal	Normal	Normal	Slight S-T depression in Leads II and III. T diphasic in Lead II	1 week	T normal in Lead I but amplitude increased
14	0.22-0.24 sec.	Low in limb leads	Normal	T flattened in Lead II	18 days	T normal in Lead I but amplitude increased
15	Normal	Low in limb leads	Normal	T waves flattened in Leads I and II	2½ weeks	None
17	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
22	Normal	Low in limb leads	Normal	T flattened in Lead II	2½ weeks	None
23	Normal	Normal	Normal	T flattened in Lead II	1 week	T normal in Lead I but amplitude increased
31	Normal	Normal	Normal	T flattened in Lead II	3 weeks	None
35	Normal	Normal	Normal	T flattened in Lead II	1 week	None
36	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months
40	Normal	Normal	0.12 sec.	Normal	None	No change in 3 months

41	Normal	Normal	0.12 sec.	Normal	Normal	None	No change in 3 months
47	Normal	Normal	0.12 sec.	Normal	Normal	None	No change in 3 months
50	Normal	Normal	0.12 sec.	Normal	Normal	None	No change in 3 months
52	Normal	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
58	0.27 sec.	Borderline in limb leads	Normal	Normal	Normal	7 weeks	QRS voltage and amplitude of T in Lead I increased
84	Normal	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
91	Normal	Normal	Normal	Normal	T wave flattened in Leads I and II	1 week	None
95	Normal	Low in limb and chest leads	Normal	Normal	T wave flattened in Leads I and II	7 weeks	None
101	Normal	Normal	0.12 sec.	Normal	Normal	None	No change in 3 months
102	Normal	Normal	Normal	Normal	T flattened in Lead II	10 days	T normal in Lead I but amplitude increased
107	Normal	Normal	Normal	Normal	S-T depressed in Leads I and II; T wave inverted in Leads I and II	6 weeks	None
119	Normal	Low in limb leads	Normal	Normal	T wave inverted in Leads II and CF ₂	3½ weeks	None
120	Normal	Low in limb leads	Normal	Normal	Inverted in Leads I, CF ₁ (normal), CF ₂ , CF ₃ , CF ₄ , and CF ₅ ; flattened in Lead II	8 days (to borderline normal)	Patient left hospital before recovery

The seven patients in the present series represent 6.1 per cent of the total number of patients studied. This is a far greater percentage than can be found in any of the normal series mentioned and must therefore be considered significant.

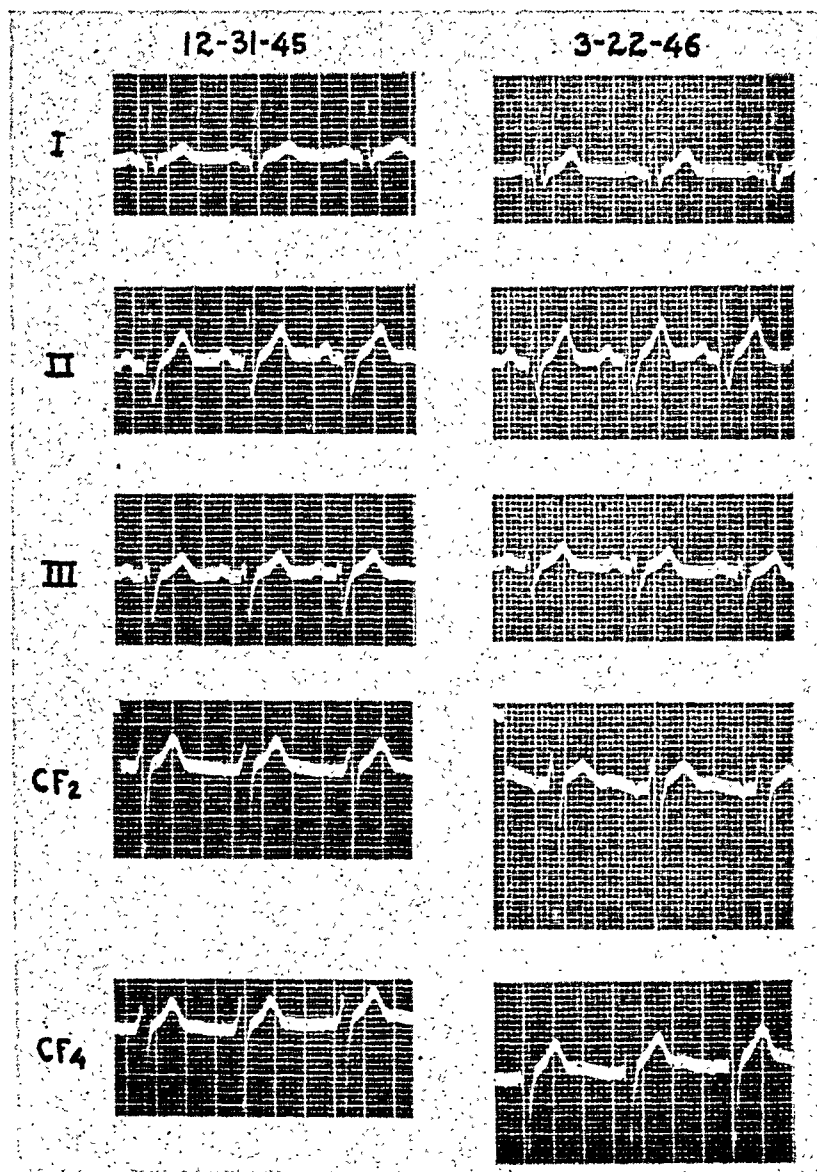


Fig. 3.—Case 17. Persistent prolongation of the QRS duration, 0.12 second. Discussed in text.

QRS Voltage.—Definite low voltage was found in six patients; in five, only the limb leads were involved (Figs. 2 and 4), while in one the chest leads also showed this change (Case 95, Table I). In one additional instance the voltage was borderline if not actually low (Fig. 1), but did show a definite increase as the record returned to normal. In no instance did the low voltage occur as the only abnormality; there were always T-wave changes as well, except in the borderline

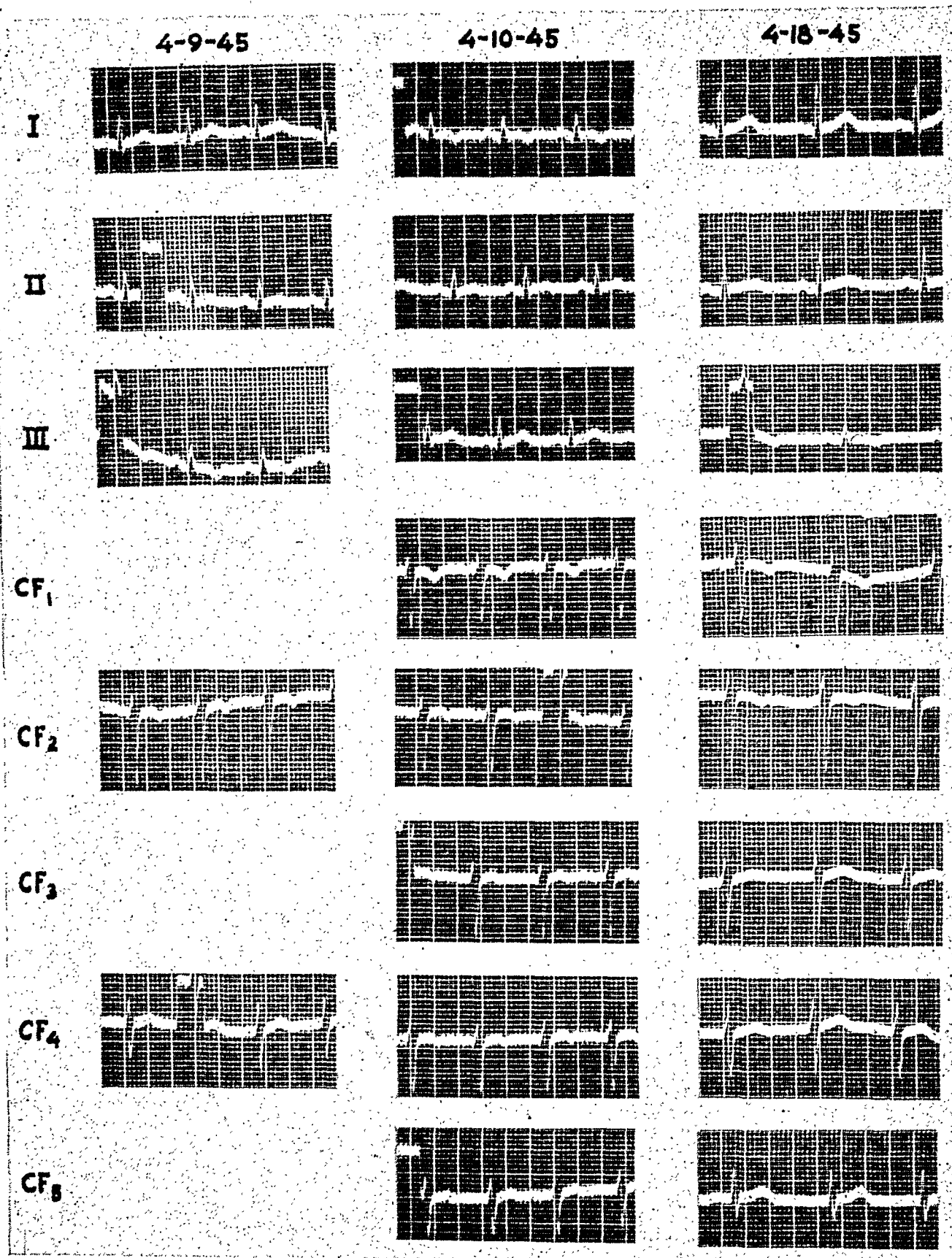


Fig. 4.—Case 120. T-wave inversion in the limb and chest leads. Low voltage of the QRS complexes. The last record still shows residual abnormalities. Discussed in text.

case which showed only a prolonged P-R interval. All of the QRS complexes showed normal voltage as the patients recovered.

RS-T Segment and T Waves.—Inverted T waves in Lead III were not considered to be abnormal since this is a well-known normal variant.

Definite T-wave changes were found in the electrocardiograms of sixteen patients (66.6 per cent). The usual change consisted of a very small, upright T wave (flattened T wave) in Lead II (Figs. 2 and 4). This occurred in thirteen patients and in eight of these was the only T-wave abnormality in the tracings, although other changes were sometimes associated (Table I). In four patients a similar T wave was present in Lead I as well as in Lead II. In one patient T-wave inversion was found in Leads I, CF₁ (normal), CF₂, CF₃, CF₄, and CF₅, while in Lead II the T wave was flattened (Fig. 4).

Inverted T waves were found in three patients (Figs. 4 and 5). In one of these there was definite S-T depression in Leads I and II with inverted T waves in the same leads. In another the inversion occurred in Leads II and CF₂. Case 120 (Fig. 4) has been discussed above. It will be noted that the only indication of T-wave abnormality in the limb leads at the time of the initial electrocardiogram was the flattened T wave in Lead II. Twenty-four hours later T-wave inversion appeared in Lead I.

It is interesting to note that in six cases the T wave in Lead I was always within normal limits, yet showed definite increased amplitude when the tracing had returned to normal (Figs. 1 and 2).

All of the changes in the RS-T segment and T waves reverted to normal in a period ranging from one to seven weeks. There was a rough correlation between the degree of abnormality and the return to normal, inverted T waves taking longer to return than flattened ones.

COMMENT

The only series of cases with electrocardiograms comparable in size to the present one is that of Reimann¹ who studied infected soldiers in a German military hospital. He reported that 75 per cent of seventy-two patients had abnormal tracings during the fifth week after the infecting meal and that the most common finding (in 58 per cent of the cases) was a flattening of the T wave without any other abnormality.

In the present series only 21 per cent of 114 patients had abnormal tracings and the abnormalities were present in the first week of the acute clinical phase of the disease. Our findings of T-wave changes in sixteen patients (66.6 per cent) are roughly in agreement with Reimann's, although in our series this was the sole abnormality in only eight cases (33.3 per cent).

Spink² reported that six of eighteen patients (33.3 per cent) had abnormalities which consisted of initial flattening or inversion of the T wave, especially in Lead II, low amplitude of the QRS complexes, and intraventricular block. Contrary to Reimann, he found the earliest changes to occur during the second week of the disease. In our series the findings are in accord with those of Spink.

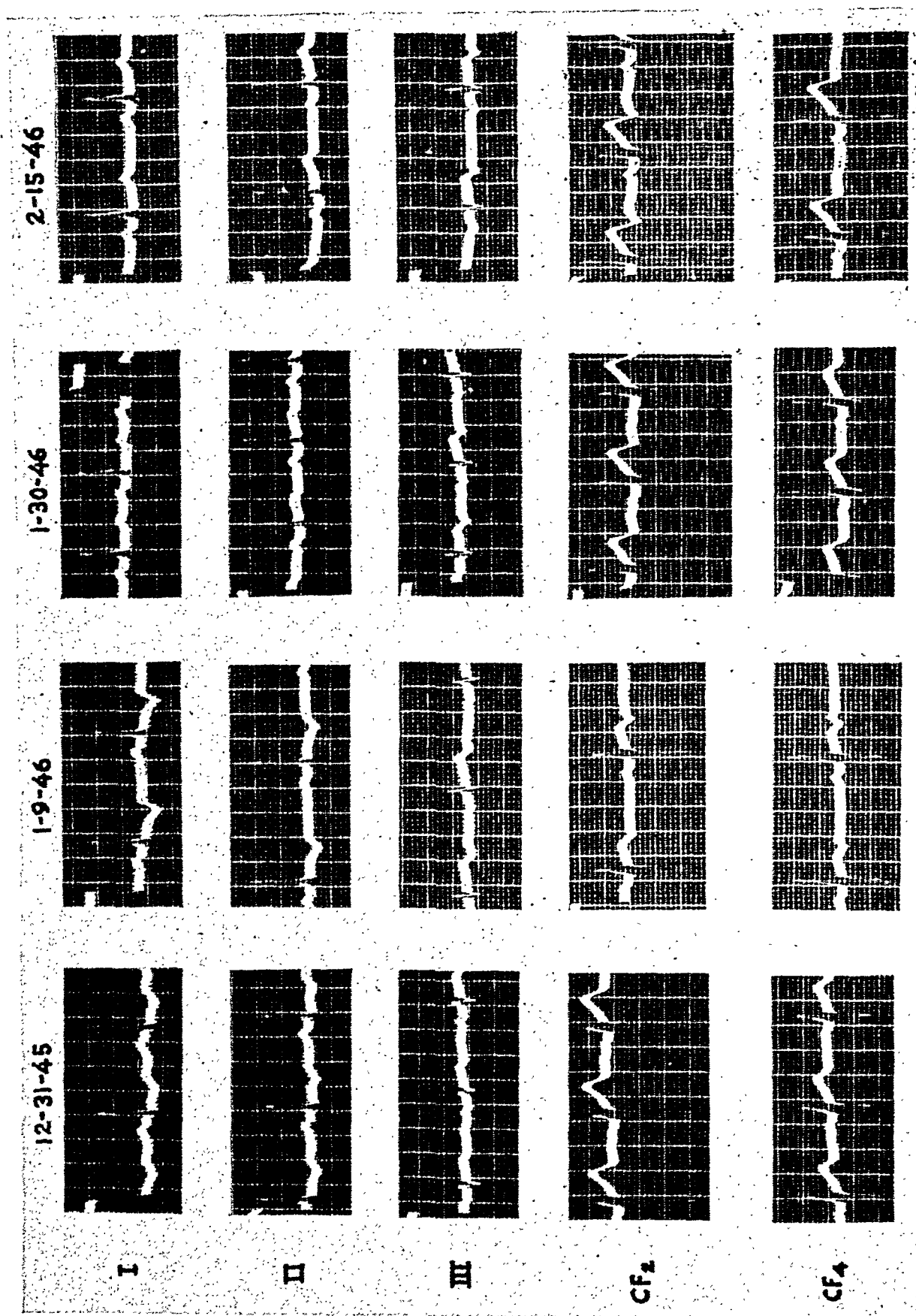


Fig 5. — Case 107. Pronounced RS-T segment and T-wave changes in Leads I and II. Discussed in text.

Among forty-four patients studied by Beecher and Amidon⁴ two showed electrocardiographic changes. One had coupled beats due to occasional nodal premature systoles (the significance of which is debatable), and the other showed a prolonged P-R interval.

Master and Jaffe³ studied four patients and found a P-R interval over 0.20 second in 25 per cent of the tracings and T-wave inversion in 33 per cent. Cushing¹³ reported one case showing T-wave inversion, and Polley and Murphy¹⁴ found low voltage of the QRS complexes with T-wave inversion in their single case. In this patient there was persistent T-wave inversion after eight months.

SUMMARY

1. One hundred fourteen consecutive cases of trichinosis were studied electrocardiographically. Definitely abnormal curves were found in twenty-four patients (21 per cent).

2. The main abnormalities consisted of changes in the RS-T segment and the T waves in sixteen patients, (66.6 per cent); prolonged QRS duration in seven patients, (29.2 per cent); low voltage of the QRS complexes in seven patients (including the one borderline case which afterward showed an increase); and prolonged P-R interval in two patients, (8.2 per cent).

3. The only abnormality which consistently occurred alone was the prolonged QRS duration, and this was the only one which did not return to normal.

4. The most common single abnormality was a flattened T wave in Lead II alone or in Leads I and II; this was found in eight patients, (33.3 per cent).

REFERENCES

1. Reimann, H.: EKG bei Trichinose, Deut. Militärarzt. 7:448, 1942, (Abstracted in Bull. War Med. 3:337, 1943).
2. Spink, W. W.: Cardiovascular Complications of Trichinosis, Arch. Int. Med. 56:238, 1935.
3. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. 31:931, 1934.
4. Beecher, C. H., and Amidon, E. L.: Electrocardiographic Findings in Forty-Four Cases of Trichinosis, AM. HEART J. 16:219, 1938.
5. Saphir, O.: Myocarditis, Arch. Path. 33:88, 1942.
6. Dunlap, G. L., and Weller, C. V.: Pathogenesis of Trichinous Myocarditis, Proc. Soc. Exper. Biol. & Med. 30:1261, 1933.
7. Goodman, S., Columbo, R., and Sachs, H.: An Epidemic of Trichinosis. In preparation.
8. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York Heart Association, New York, 1940.
9. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, AM. HEART J. 27:524, 1944.
10. Ferguson, D. O., and O'Connell, J. T.: Cardiovascular Observations: Electrocardiograms of Men Without Heart Symptoms, U. S. Nav. M. Bull. 24:860, 1926.
11. Shipley, R. A., and Halloran, W. R.: The Four-Lead Electrocardiogram in Two Hundred Normal Men and Women, AM. HEART J. 11:324, 1936.
12. Hall, G. E., Stewart, C. B., and Manning, G. W.: The Electrocardiographic Records of 2,000 RCAF Aircrew, Canad. M. A. J. 46:226, 1942.
13. Cushing, E. H.: Electrocardiographic Changes in Trichinosis, AM. HEART J. 11:494, 1936.
14. Polley, T. Z., and Murphy, F. D.: Cardiac Involvement in Trichinosis: Report of a Case in Which There Were Electrocardiographic Changes, AM. HEART J. 27:266, 1944.

DISEASES ASSOCIATED WITH LOW CAPILLARY RESISTANCE

EDWARD E. BROWN, M.D.
ASHLAND, ORE.

BLEEDING is a symptom which arrests attention. Nosebleeds in rheumatic or hypertensive patients, menorrhagia in purpura, and severe bleeding which follows an operation or minor injury can cause deep concern to both patient and physician. Individuals who show a bleeding tendency usually have a low capillary resistance. The lower the capillary resistance, the greater is the bleeding time.¹ Although some causes of capillary fragility are known, our knowledge on the subject is far from complete.

An analysis is presented of diseases or symptoms found to be present in sixty patients on the day their capillary resistance was extremely low (5 cm. of mercury suction). Solely because of their marked capillary fragility, these sixty patients were chosen for review from among 580 patients in a general practice upon whom some 3,000 capillary resistance determinations were routinely performed. Analysis of these symptoms is given for what light it may shed on factors responsible for undue bleeding.

Capillary resistance was determined with a suction cup apparatus previously described.² The minimal amount of negative pressure (suction), applied for one minute to the antecubital space, which produces one petechia or more, is the capillary resistance of the individual. Intervals of 5 cm. of mercury are used, readings being taken from a vacuum gauge. Normal values for capillary resistance are 20 cm., or higher. Definite fragility of capillaries exists when petechiae are produced at 10 cm. of suction, and fragility is extreme when petechiae are produced at a suction of 5 cm. of mercury.

Low capillary resistance has been recorded in scarlet fever,^{2,3} measles,⁴ scurvy,⁵⁻⁸ rheumatic fever,^{9,10} thrombocytopenic purpura,^{1,11} allergic purpura,¹² allergy,¹³ asthma,¹⁴ bronchopneumonia,¹⁵ ulcer¹⁶ and colitis,¹⁶ hypertension,^{17,18} myxedema,¹⁹ diabetes,¹⁸ during menses or in the premenstrual phase,^{20,21,28} and with increasing age.^{2,18,22-24}

Extremely low values, 5 cm., have been noted in toxic scarlet fever, early measles, and in the acute stages of purpura and rheumatic fever.

Summaries are presented on sixty patients, all showing extreme capillary fragility (5 cm.) on at least one occasion (Table I). The word "negative" in the column Symptoms on Day of Low Capillary Resistance is used to signify that no symptoms or signs were noted on that particular day to account for the low capillary resistance obtained. Dates are included mainly to allow the reader a chance to interpret a possible sequential relation of disease to capillary resistance.

TABLE I. CLINICAL FINDINGS IN SIXTY PATIENTS WHO SHOWED DECREASED CAPILLARY RESISTANCE ON AT LEAST ONE OCCASION

CASE	SEX	AGE	PAST HISTORY	DATE OF LOW CAPILLARY RESISTANCE (5 CM.)	SYMPTOMS ON DAY OF LOW CAPILLARY RESISTANCE	NUMBER OF OTHER CAPILLARY RESISTANCE READINGS	RANGE OF OTHER CAPILLARY RESISTANCE READINGS (CM.)
1	M	29	Rheumatic fever, age 16	2/19	Subacute rheumatic fever; urticaria	—	—
2	F	33	Recurrent tonsillitis; sinusitis	9/1	Evanescant pain in legs	—	—
3	M	35	Rheumatic myocarditis; recurrent tonsillitis and sinusitis; bronchopneumonia 3/1	3/24	Negative; ambulant, recovered from bronchopneumonia	2	10-20
4	F	32	Metrorrhagia	1/23	Gastroenteritis; sinusitis; several petechiae on skin	3	10-15; average 10
5	F	38	Severe rheumatic fever and myocarditis, age 19; menorrhagia; bruises easily	3/16	Aching generally; many petechiae (more than 60)	18	10-30; average 15
6	F	17	Chorea; mitral insufficiency	9/15	Rheumatic pains	6	10-20; average 15
7	M	40	Hay fever; rheumatic pains	2/2	Subacute rheumatic fever	2	15-20
8	F	47	Neurasthenia	10/31	Rheumatoid arthritis; fatigue	1	30
9	F	62	Hypertension	1/2	Hypertension (204/162); joint pains; bruises	—	—
10	F	59	Rheumatic pains; prolonged bleeding; hemorrhagic retinitis 1/24; angioneurotic edema	2/7	Rheumatic pains; acute sinusitis; several petechiae	—	—
11	F	43	Rheumatic mitral insufficiency and stenosis	3/3	Aching; many petechiae	—	—
12	F	30	Rheumatic pains	4/14	Rheumatic pains	—	—
13	F	27	Negative	5/29	Negative	—	—
14	F	60	Hay fever; rheumatoid arthritis; recent bruising	7/16	Nosebleed; sinusitis; joint pain	—	—
				8/10	Joint pains; hypertension (180/110); several petechiae	—	—
15	F	34	Easy bruising; obesity	8/13	Sinusitis; joint pains; percussion of sinuses produces hematoma	—	—
16	F	36	Bruises and bleeds easily; rheumatic pains	8/13	Rheumatism; fatigue; headache; sinusitis	—	—
				12/5	Rheumatic pains; neurasthenia	—	—

TABLE I—(Cont'd)

CASE	SEX	AGE	PAST HISTORY	DATE OF LOW CAPILLARY RESISTANCE (5 CM.)	SYMPTOMS ON DAY OF LOW CAPILLARY RESISTANCE	NUMBER OF OTHER CAPILLARY RESISTANCE READINGS	RANGE OF OTHER CAPILLARY RESISTANCE READINGS (CM.)
33	F	47	Negative	2/14	Hypertension (190/110)	—	—
34	F	46	Menorrhagia; hypertension; recent menopausal symptoms	1/16	Hypertension (220/116); no menses 3 months	2	10-15
35	F	67	Rheumatism; hypertension; cerebral hemorrhage, age 65; following limited diet, developed scurvy; spontaneous bruises of hands	11/17	Scurvy; fragility continues despite ingestion of 4 oranges daily in past 3 weeks; hypertension (260/160)	—	—
36	F	46	Eczema neck and ear; vertigo and hives following ingestion of many foods; chronic sinusitis; easy bruising	2/28	Vertigo; deafness; tinnitus; many petechiae	7	10-15; average 10
37	F	31	Chronic fatigue; mental depression; chronic sinusitis	5/20	Vertigo; tinnitus; marked fatigue; hypotension (100/64)	8	10-20; average 10
38	M	46	Late latent syphilis	9/14	Fatigue	14	15-40; average 25
39	F	31	Eczema lids; hypertrichosis; numerous lentigines and moles; bruises easily	1/17 1/25 3/10	Depressed Fatigue Fatigue	—	—
40	F	22	Tachycardia; precordial stabs; vertigo; chronic fatigue; menorrhagia	5/5 5/3 5/11 4/17	Negative; depressed Negative; several petechiae Fatigue; mild migraine today; few petechiae	—	—
41	M	38	Recurring peptic ulcer	7/21	Peptic ulcer; 10 petechiae on skin	—	—
42	M	39	Fatigue; sinusitis; easy bruising and bleeding	6/11	Vertigo; tinnitus	—	—
43	F	31	Rheumatic fever, age 11; mitral insufficiency; generalized pains; hay fever	2/6	Vertigo; edema hands; urine, blood pressure, negative; 7 months pregnant	4	15-20; average 15
44	M	35	Various allergies; numerous lentigines	4/5	Hives; several petechiae; epinephrine 1:1000, m. 5, injected subcutaneously; 15 minutes later, capillary resistance 15 cm.	—	—

45	F	28	Migraine; rheumatic pains	3/25	Migraine; 15 minutes after ampule gynergen, capillary resistance 10 cm.	—	—
46	F	46	Acne rosacea; metrorrhagia	3/18	Premenstrual; several petechiae and telangiectases	20	10-25; average 15
47	F	31	Frequent colds	2/28	First day of menses; 5 petechiae	—	—
48	F	30	Negative	6/3	Premenstrual	—	—
49	M	42	Undiagnosed hematemesis requiring 13 blood transfusions in two weeks, at age 40	3/29 4/3 4/10	Acute rhinitis Negative Negative; 4/16 capillary resistance 10 cm.	7	10-30; average 15
				4/25	Negative; splenectomy 6/14, diagnosis Banti's syndrome; capillary resistance 6 days later (6/20) 30 cm.		
50	F	47	Chronic sinusitis; progressive deafness	2/28	Tinnitus; 4 petechiae	—	—
51	F	32	Menorrhagia; metrorrhagia	10/31	Negative; few petechiae	11	10-20; average 15
52	F	42	Thyroidectomy age 38; hyperthyroidism continues	3/23	Hyperthyroidism; asthmatic bronchitis; many petechiae	—	—
53	F	32	Bilateral oophorectomy, age 28; joint pain; bleeds readily; sinusitis; purpuric reaction at site of injection (cold vaccine)	11/26 1/10	Negative; blood pressure 106/70 Negative; few petechiae on skin	—	—
54	M	45	Bled 24 hours after extraction of tooth; bruises	2/6	Negative	2	10-10
55	F	26	Bleeds and bruises readily; menses 6 days duration	5/18	Negative; 5 petechiae	1	20
56	F	29	Rheumatic mitral insufficiency; numerous lentiginos; anemia	5/29	Early tubal pregnancy with rupture and staining since 4/18	—	—
57	F	45	Recent amenorrhea	10/29 11/6 11/8	Negative Negative; not pregnant Negative; ulcer cervix; moderate leukorrhea	—	—
58	F	28	Negative			—	
59	F	50	Cancer rectum; metastasis to liver	10/12	Negative except as noted in history	4	10-20; average 15
60	M	49	Rheumatoid arthritis; asthma	4/3	Negative; more than 40 petechiae	—	—

OBSERVATIONS

Sixty patients exhibited several symptoms or diseases which may or may not have been related to their extreme capillary fragility. These will be briefly discussed.

Rheumatic Pain.—Seventeen complained of joint or muscle pain, usually vague and fleeting, on the day low readings (5 cm.) were obtained. Eleven additional patients gave a history of rheumatic fever or recurring generalized pains. Thus a total of twenty-eight of the sixty patients had, on the day of the low reading or previously, rheumatic or generalized pains. Other patients with rheumatic pain, not included in this report, had either normal or moderately lowered (10 cm.) capillary resistance. In a previous study dealing with ambulant rheumatic children,⁹ values of 5 cm. were not uncommon, and abnormal resistances (5 and 10 cm.) were found in 40 per cent of all capillary resistance determinations in February, in contrast to only 5 per cent abnormal resistances in September.

Acute Upper Respiratory Infection.—Nine patients had symptoms suggesting these conditions at the time of the low readings. In five others (included in the rheumatic group discussed in the preceding paragraph) there were also joint and muscle pains.

Hypertension.—Systolic blood pressures of more than 170 mm. mercury were found in four; in two others (included in rheumatic group) there were also joint or muscle pains.

Fatigue.—This was complained of by eight patients. Associated complaints in four of these patients were noted, once each, as follows: rheumatic pains, rheumatoid arthritis, acute sinusitis, and migraine.

Vertigo and/or Tinnitus.—These symptoms were complained of by four patients; several others gave a history of these complaints.

Migraine.—Marked capillary fragility during migraine attacks occurred in two patients (Cases 40 and 45), in one of whom there was associated fatigue.

Allergy.—Hives existed in two patients when low readings were found; one had associated joint pains. In the other (Case 44) capillary resistance rose from 5 to 15 cm. fifteen minutes after injection of five minims of adrenalin.

Menses.—One woman was in the first day of her menstrual flow; two other women were in the premenstrual phase (within two days of the expected menses). Many others were tested both during menses and in the premenstrual phase. Normal values were usually encountered; not uncommonly low capillary resistances (10 cm.) existed, but these cases are omitted since minimal values (5 cm.) were not reached.

Bruising and Bleeding.—Ecchymoses as a result of insignificant trauma were noted on the skin of five patients at the time their low capillary resistance was

found. One of the patients had scurvy and another had a proved Banti's syndrome. A history of easy bruising or bleeding was obtained in twenty-one others. Such history included menorrhagia, metrorrhagia, prolonged bleeding following tooth extraction or shaving, spontaneous nosebleeds, and retinal hemorrhage (Case 32).

Petechiae.—More than three petechiae were present on various parts of the skin in twenty-two of sixty patients; of these patients seven showed four to nine petechiae, eight showed ten to thirty petechiae and seven had more than thirty petechiae. Subacute bacterial endocarditis was not present in any of these patients.

Telangiectases.—Two patients had telangiectases of the face.

Miscellaneous Conditions.—A single instance of marked capillary fragility was found in a young man whose chief complaint was an acute petechial rash of the face associated with acute pharyngitis (Case 20). In another patient marked fragility existed with afebrile pleurisy (Case 29).

Seasonal Variations.—Marked capillary fragility occurred more often in the winter and spring, forty of sixty low readings occurring in the first six months of the year. A corresponding seasonal variation in capillary resistance has been previously reported.^{9,27}

CONCLUSIONS

1. One may observe marked capillary fragility quite commonly. It existed on at least one occasion in sixty of 580 unselected patients on whom some 3,000 capillary resistance determinations were made.
2. Infection, either low-grade or acute, was often present at the time when low capillary resistance was noted. The most common accompanying condition was vague, indefinite joint and muscle pains. Less commonly acute upper respiratory infections were present.
3. Twenty-three of the sixty patients gave a history of easy bleeding or bruising, or both.
4. Associated conditions noted in patients with extreme capillary fragility were, in approximate order of frequency, fatigue, hypertension, vertigo, allergy, and menstruation.
5. For unknown reasons the degree of capillary fragility is variable in the same person from time to time.
6. There is as yet no satisfactory explanation for the marked capillary fragility existing in many patients.

REFERENCES

1. Elliott, R. H. E.: The Suction Test for Capillary Resistance in Thrombocytopenic Purpura, J. A. M. A. 110:1177, 1938.
2. Brown, E. E.: Capillary Resistance in Scarlet Fever, Arch. Pediat. 57:553, 1940.
3. Colarizi, A.: The Morphology and Capillary Resistance in Scarlet Fever—Studies in Connection With the Schultz-Charlton Blanching Phenomenon, Clin. pediat. 17:585, 1935.

4. Jaso, E.: Test of Provoked Purpura in Children—Capillary Resistance in Measles, *Pediatría españ.* 21:396, 1932.
5. Hess, A. F.: The Blood, the Blood Vessels and the Diet, *Am. J. Dis. Child.* 8:386, 1914.
6. Göthlin, G. F.: A Method of Establishing the Vitamin C Standard and Requirements of Physically Healthy Individuals by Testing the Strength of Their Cutaneous Capillaries, *Arch. f. Physiol.* 61:225, 1931.
7. Öhnell, H.: Experiences of Endemic, Manifest and Latent Scurvy in Sweden With Special Reference to New Methods of Diagnosing Latent Scurvy, *Acta med. Scandinav.* 68:176, 1928.
8. Dalldorf, Gilbert: A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* 46:794, 1933.
9. Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, *J. Pediat.* 18:328, 1941.
10. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, 1931, Williams & Wilkins Company, p. 43.
11. Jones, H. W.: A Simple Test for Capillary Resistance: The "Flicking" Test, *Am. J. M. Sc.* 185:535, 1933.
12. Diamond, J.: Anaphylactoid or Allergic Purpura, *J. Pediat.* 8:697, 1936.
13. Rackemann, F. M.: Clinical Allergy, Particularly Asthma and Hay Fever, Mechanism and Treatment, New York, 1931, The Macmillan Co.
14. Gold, Harry: Use of Drugs in the Treatment of Allergic Conditions, *Conferences on Therapy, J. A. M. A.* 112:1335, 1939.
15. Gorini, P.: Capillary Studies in Acute Pulmonary Illnesses of Infants, *Lattante* 9:64, 1938.
16. Schultzer, P.: Studies on Capillary Resistance; Lowered Resistance Due to Vitamin C Deficiency and Other Conditions in Hospitalized Patients, *Acta med. Scandinav.* 81:113, 1934; cited by Roberts and others.²⁷
17. Griffith, J. Q., Jr., and Lindauer, M. A.: Increased Capillary Fragility in Hypertension: Incidence, Complications, and Treatment, *AM. HEART J.* 28:758, 1944.
18. Beaser, S. B., Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes Mellitus, Hypertension and Age, *Arch. Int. Med.* 73:18, 1944.
19. Lange, Kurt: Capillary Permeability in Myxedema, *Am. J. M. Sc.* 208:5, 1944.
20. Petersen, W. F., and Willis, D. A.: Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister, *Arch. Int. Med.* 38:663, 1926.
21. Brewer, J. I.: Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation, *Am. J. Obst. & Gynec.* 36:597, 1938.
22. Cutter, I. S., and Marquardt, G. H.: Studies in Capillary Fragility, *Proc. Soc. Exper. Biol. & Med.* 28:113, 1930.
23. Abt, A. F., Farmer, C. I., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* 8:1, 1936.
24. Kugelmass, I. N.: Vitamin P in Vascular Purpura, *J. A. M. A.* 115:519, 1940.
25. Corn, A. M., and Brown, E. E.: Oral Manifestations of Systemic Disease in an Acromegaly Case (Case Report), *J. D. Soc. (N. Y.)* 9:61, 1943.
26. Brown, E. E.: Lentigines; Their Possible Significance, *Arch. Dermat. & Syph.* 47:804, 1943.
27. Roberts, L. J., Blair, R., and Bailey, M.: Seasonal Variations in Capillary Resistance of Institutional Children, *J. Pediat.* 11:626, 1937.
28. Brown, E. E., and Wasson, V. P.: Capillary Fragility and Menses in Rheumatic Girls, *J. Pediat.* 30:455, 1947.

THE ELECTROCARDIOGRAM IN MAN DURING AN EPISODE OF CHILL AND FEVER INDUCED BY INTRAVENOUS TYPHOID VACCINE

A. S. FREEDBERG, M.D., M. J. McMANUS, B.S., AND
M. D. ALTSCHULE, M.D.
BOSTON, MASS.

THE recent medical literature shows evidence of a growing interest in the cardiovascular changes which occur during the course of infections. Published studies of the electrocardiographic alterations during infections are numerous.¹⁻⁸ The changes consist of shortening or prolongation of the P-R interval, decrease in voltage of the QRS complex, a relative increase in the Q-T interval, and alterations in the T wave and S-T segment. The interpretations of the latter changes have neglected the effects of fever, heart rate and position, alterations in acid-base balance, and many other influences. In published clinical studies, furthermore, it is often impossible to distinguish the effects of fever, *per se*, from those of myocardial changes due to infection itself, anoxia, salt and water depletion, malnutrition, and other unknown factors.

Reports^{9,10} based on studies made during physically induced fevers do not yield comparable data, for fevers so induced do not pass through the four phases of the febrile reaction to infection.¹¹ Physically induced fever lacks the initial prodrome and chill phases characteristic of the febrile reaction to disease;¹² in the chill phase, pronounced vasoconstriction in the skin, kidney, and brain, decreased cardiac output, and increased arteriovenous oxygen difference occur.

It is, therefore, considered of interest to report a study of electrocardiograms obtained during the course of fever induced by typhoid vaccine in human subjects.

MATERIAL AND METHODS

Nine subjects, six of them men, varying in age from 25 to 63 years, were given typhoid vaccine intravenously for therapeutic purposes. The diagnoses were rheumatoid arthritis (Cases 1, 2, 4, 8, 9); tabes dorsalis and general paresis (Cases 5, 7), lymphedema of the face of unknown etiology (Case 6), and subacute bacterial endocarditis (Case 3). In six patients (Cases 1, 4, 5, 6, 8, 9) no evidences of cardiac or pulmonary disease were present. In Case 2, a primary adenocarcinoma of the right lower bronchus with atelectasis and bronchiectasis was

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

This study was aided by a grant from the Josiah Macy Jr. Foundation.

Received for publication Nov. 6, 1946.

present; no evidence of heart disease was found. In Case 7, x-ray examination showed moderate cardiac enlargement and aortic dilatation and tortuosity. In Case 3, subacute bacterial endocarditis, rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, cardiac enlargement, and normochromic anemia were present. The studies were made under basal conditions. The patients were recumbent at an angle of approximately 15° with the electrodes in place throughout the experiment; the routine limb and IV F leads were recorded before the injection of the vaccine, and at varying periods thereafter.

Electrocardiograms were taken in each of the four phases of the febrile reaction: (1) prodrome, (2) chill, (3) flush, and (4) defervescence. In two instances 100 per cent oxygen was administered by means of a Boothby mask, at a rate of 10 liters per minute, beginning ten minutes before the injection of vaccine and continuing throughout the febrile course.

The electrocardiograms were corrected for errors in standardization. Bazett's formula $K = \frac{\text{Systole}}{\sqrt{R-R}}$ was used for calculating electrical systole. To de-

termine heart rate, height of P, P-R interval, and, in Lead IV F, the height of T, six to ten complexes were measured and the results averaged. The areas of the QRS and T waves in Leads I, II, and III were measured from photographically enlarged records¹³ and/or with a $\times 10$ ocular¹⁴ from the original records. The desired vectors were then obtained from a modified Dieuade chart. In one instance (Case 1) Leads I and III were taken simultaneously. The definition of symbols used in this paper are as follows:

A represents net area of the QRS, T, or QRS-T complex.

\hat{A} represents the vector QRS, T, or QRS-T, representing both magnitude and direction.

G and $\hat{A}G$ = manifest area of QRS-T, and magnitude and direction of QRS-T, respectively.

$\hat{A}G$ and $\hat{A}QRS-T$ are referred to as the ventricular gradient.

m.v.s. = microvolt-seconds.

RESULTS

Heart Rate.—The control rates varied from 58 to 75 in eight patients; in one patient (Case 3) the rate was 102 per minute. These were unchanged during the prodrome. In three instances at the onset of the chill phase sinus bradycardia was observed. After the onset of fever late in the chill phase, and in the flush phase, an average rise in pulse rate of ten beats per minute per degree Fahrenheit rise in body temperature occurred. In defervescence the average increase in cardiac rate above the control was 7.7 beats per minute per degree Fahrenheit elevation in body temperature.

P Wave and P-R Interval.—The control P-R intervals varied from 0.15 to 0.18 second, and the height and form of the P waves were normal. No significant changes were observed during any of the febrile phases.

The Relative Duration of Electrical Systole.—The control values for K varied from .390 to .408 in eight patients. In Case 3 the control value for K was .425. No changes were observed during the prodrome. In the chill phase, in all instances except Case 7, the value for K was increased. During the flush phase K

was increased in all instances as compared to the control; but was variable as compared with the chill, being unchanged in three, increased in five, and decreased in two instances (Table I). The greatest increase in K was from .400 to .447 (Case 1). In defervescence the value for K showed a return toward the control in all instances.

T Wave in Lead IVF.—No changes were observed during the prodrome. In the chill phase a decrease in the height of the T wave was observed in six of eight instances, ranging from 2 to 3 millimeters. In one instance (Case 8) the T wave during the chill phase was biphasic. Changes in the S-T segment during the chill phase were slight, the maximum being a depression of 0.5 millimeters. These changes were still present in the flush and defervescence phases (Fig. 1).

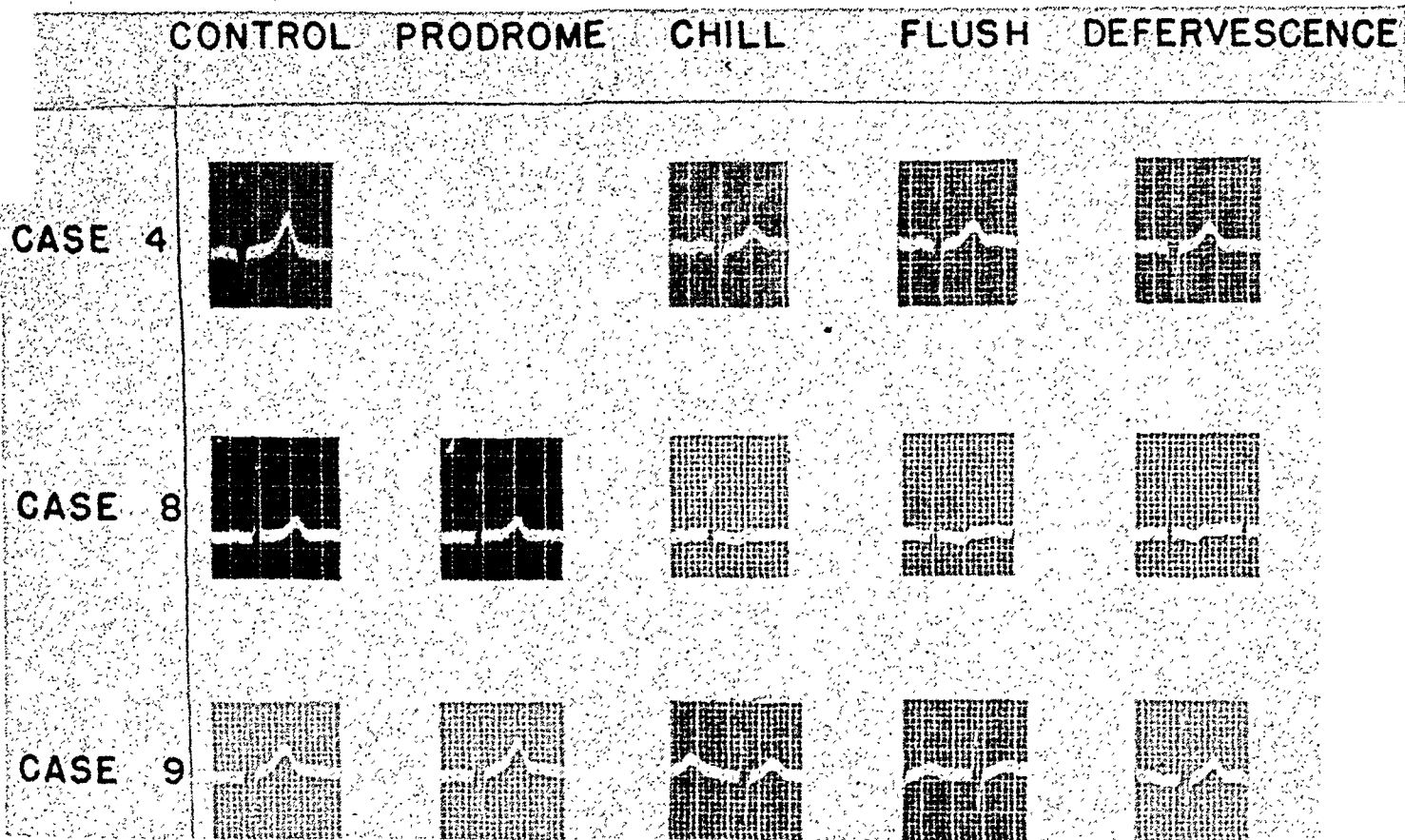


Fig. 1.—Lead IVF obtained during the various phases of a febrile reaction. In Case 4 the T wave is decreased in height during the chill, flush, and defervescence phases. In Case 8 slight depression of the S-T segment and a biphasic T wave are present in the chill and flush phases. The S-T segment is isoelectric in defervescence. In Case 9 the T wave is decreased in height in the flush as compared with the chill phase; a return toward the control is present during defervescence.

The Manifest Net Area and Direction of QRS-ÂQRS.—The control ÂQRS varied from $+20^{\circ}$ to $+69^{\circ}$ in eight patients. It pointed to the left of ÂG in four and to the right in four instances, the extremes being 3° to 17° in the former and 5° to 34° in the latter instances (Table I, Fig. 2). No changes were observed during the prodrome. The change in direction of ÂQRS during the chill phase was slight (Table I, Fig. 2). Compared with the control and chill phase, there

were no changes during the flush phase except in Case 9, in which there occurred a rotation of 43 degrees to the left from its position in the chill phase (Table I, Fig. 2). The control AQRS varied from 8 microvolt-seconds to 39 microvolt-seconds. This value decreased in the chill phase 5 to 15 microvolt-seconds in five cases and increased 3 to 4 microvolt-seconds in three cases. In the flush phase, as compared with the chill phase, AQRS decreased in all instances, except Case 2; from 3.0 to 10.0 microvolt-seconds, the average being 5.7 microvolt-seconds. The average percentile decrease was 32.7. AQRS showed a return to or toward the control values in all instances during defervescence.

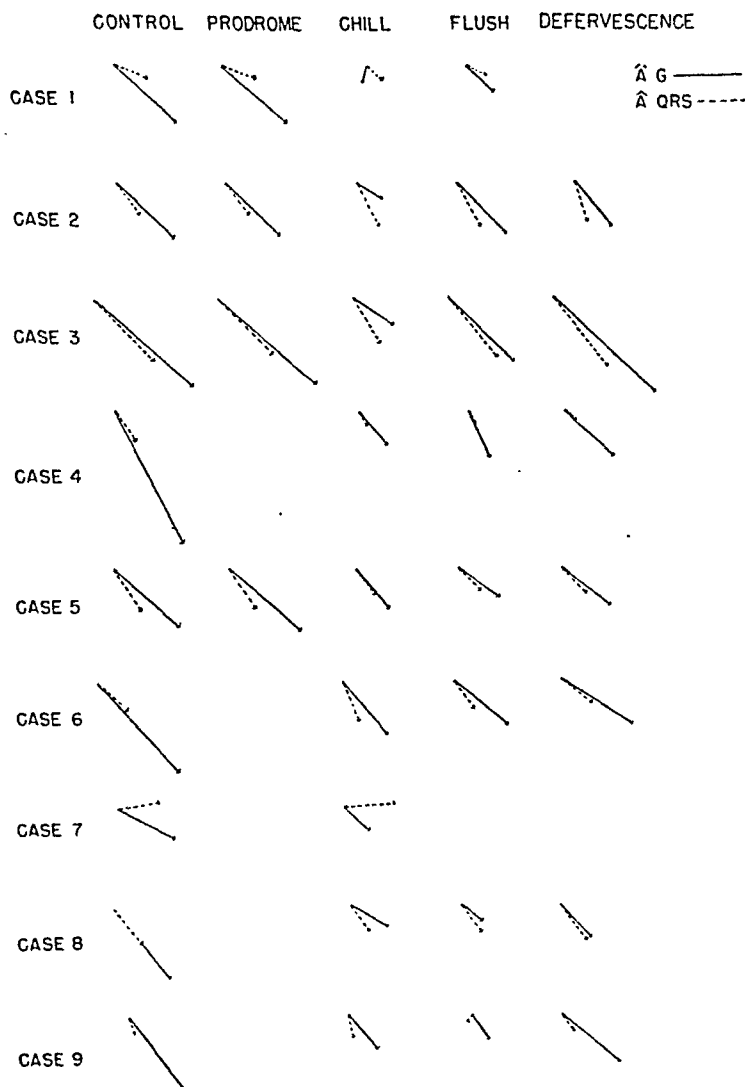


Fig. 2.—The relation between $\hat{A}qrs$ and $\hat{A}G$ during the various phases of a febrile reaction.

The Manifest Net Area and Direction of $T-\hat{A}T$.—The control values for $\hat{A}T$ varied from 17 to 48.5 microvolt-seconds and $+20^\circ$ to $+64^\circ$. No changes were observed during the prodrome. There was a decrease in magnitude and a change in direction of $\hat{A}T$ in all instances in the chill phase, represented in the electrocardiogram by a decrease in the height of T waves and/or a depression of the S-T segment (Table I and Figs. 3, C and D, 4B, and 5). Minor alterations

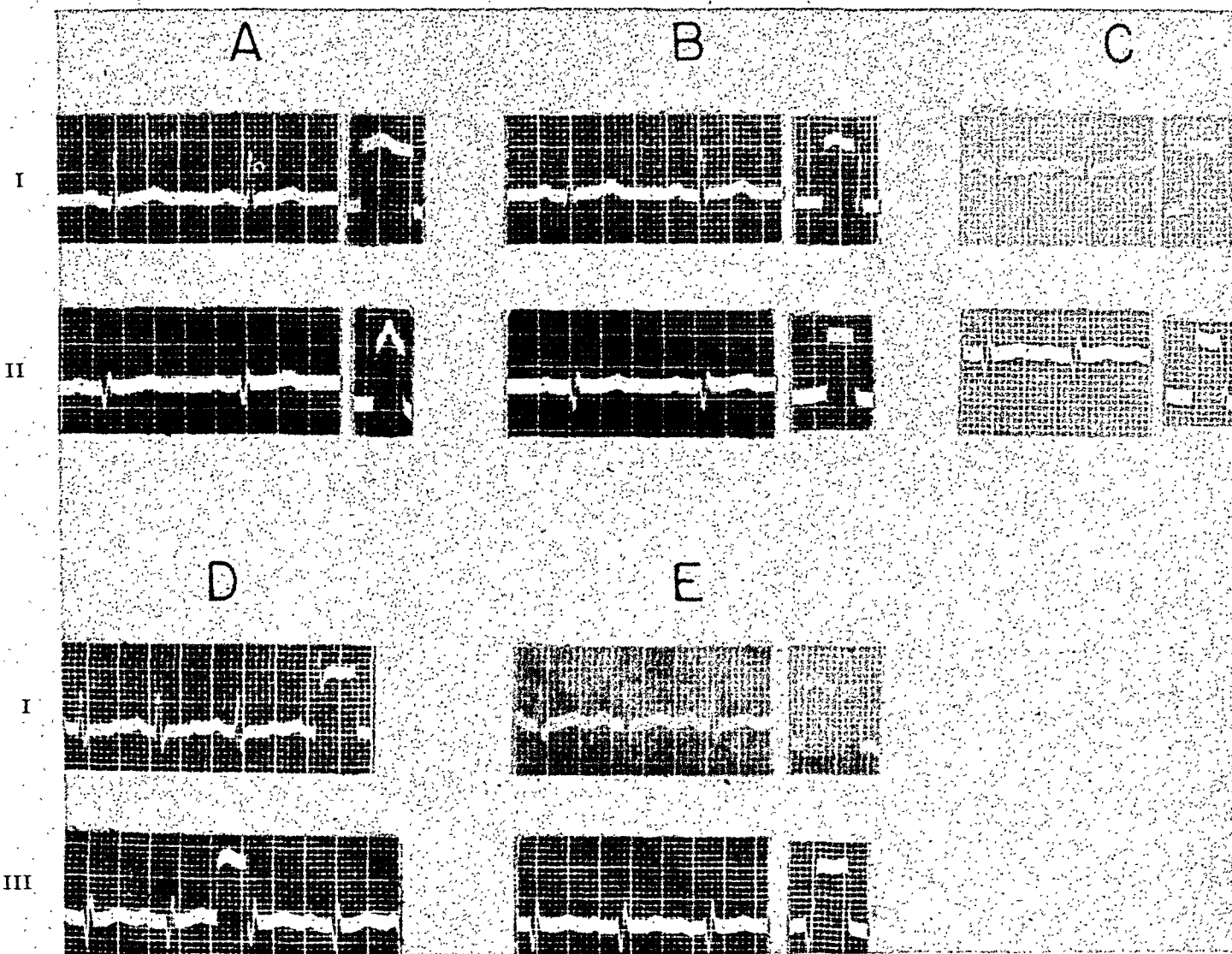


Fig. 3.—The electrocardiogram in Case 1. Leads I and III were taken simultaneously. A, control; B, prodrome; C, moderate chill phase; D, late chill phase; and E, flush phase.

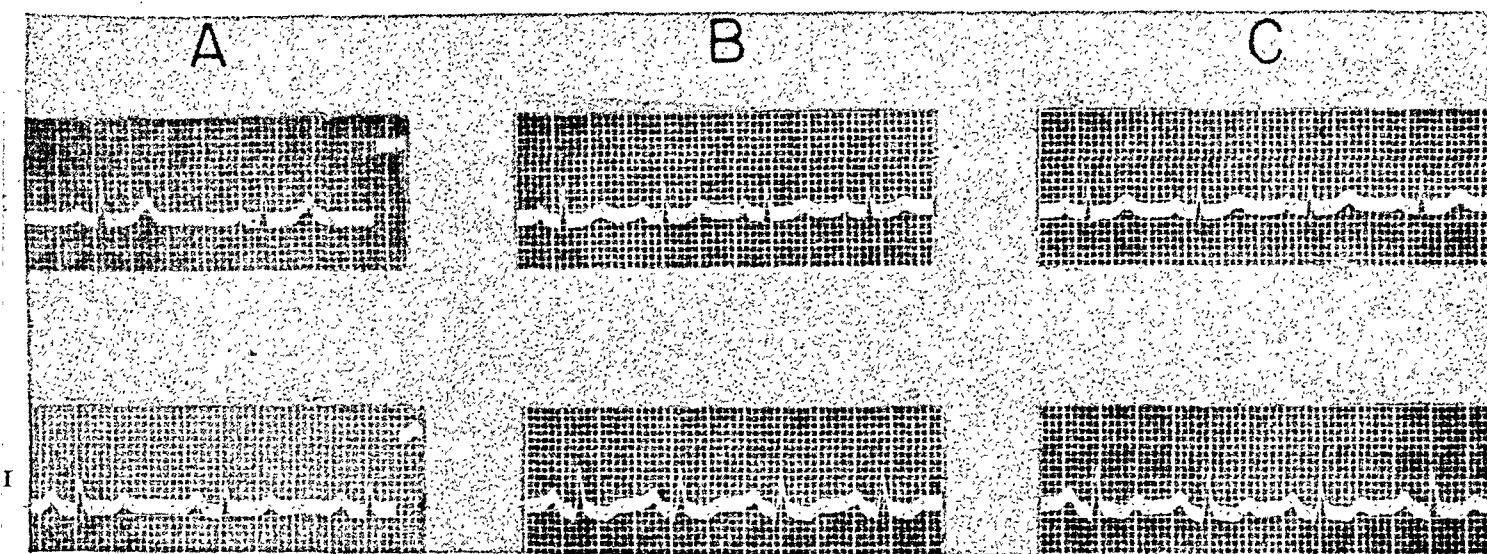


Fig. 4.—The electrocardiogram in Case 2 during a febrile episode. A, control; B, chill phase; and C, flush phase.

TABLE I. MEASUREMENTS OF THE CARDIAC RATE RELATIVE DURATION OF ELECTRICAL SYSTOLE AND THE VENTRICULAR GRADIENT IN FEVER
INDUCED BY TYPHOID VACCINE

CASE	RATE PER MIN.	$K = \frac{QT}{\sqrt{R-R}}$	\hat{A}_{QRS}		\hat{A}_T		\hat{A}_G		CHANGE IN \hat{A}_{QRS}	CHANGE IN G	CHANGE IN RATE	TEMP.	REMARKS
			M.V.S.	DEGREE	M.V.S.	DEGREE	M.V.S.	DEGREE	(PER CENT)	(PER CENT)	(PER CENT)		
1	70	.406	17.0	+20	21.0	+55	38.0	+40	—	—	—	98.6	Control
	73	.400	17.0	+17	23.0	+51	39.0	+38	—	+2.6	+4.3	98.6	Prodrome
	107	.427	12.0	+21	2.0	+129	12.0	+32	-29.4	-68.5	+53.	100.4	Mod. chill
	118	.447	9.0	+42	8.0	+180	8.0	+108	-47.0	-79.0	+68.5	102.0	Late chill
	111	.434	11.0	+24	6.0	+60	16.5	+39	-35.2	-56.5	+58.6	103.5	Flush
2	73	.407	18.0	+50	17.0	+35	35.0	+42	—	—	—	98.2	Control
	72	.407	18.0	+50	12.0	-70	35.5	+42	+22.2	-58.5	+46.5	98.2	Prodrome
	107	.415	22.0	+60	9.0	-5	14.5	+30	-30.6	-8.6	+49.2	101.0	Chill
	109	.415	23.5	+60	11.0	+10	32.0	+45	+5.5	-22.8	+32.8	102.4	Flush
	97	.407	19.0	+70	11.0	+10	27.0	+50	+5.5	-22.8	+32.8	101.2	Defervescence
3	102	.425	39.0	+43	21.5	+35	60.0	+40	—	—	—	99	Control
	102	.425	38.0	+43	9.5	-65	60.0	+40	—	—	—	99	Prodrome
	116	.445	24.0	+57	6.0	-10	21.0	+32	-38.4	-65.	+13.7	104	Chill
	136	.450	36.0	+48	23.5	-29	42.0	+43	-8	-30	+33	105.2	Flush
	110	.435	40.0	+50	23.5	-29	64.0	+42	+2.6	+7	+7.8	102.5	Defervescence
4	58	.408	17.0	+55	48.5	+63	66.0	+61	—	—	—	98.0	Control
	96	.407	8.0	+55	13.0	+42	20.0	+49	-53	-70	+65.5	101.2	Chill
	98	.417	7.0	+60	15.0	+61	23.0	+62	-59	-65	+69	102.0	Flush
	83	.410	8.0	+37	22.0	+41	30.0	+40	-53	-54.5	+43	101.6	Defervescence
5	68	.405	23.0	+55	19.0	+20	42.0	+40	—	—	—	98.5	Control
	68	.405	22.0	+55	7.0	+40	44.0	+40	-30	-45	+21	98.5	Prodrome
	82	.407	16.0	+50	8.5	+14	23.0	+48	-35	-45	+29	101.2	Chill
	88	.413	15.0	+43	10.0	+28	23.0	+34	-26	-36	+40	102.3	Flush
	95	.402	17.0	+42	10.0	+28	27.0	+37	-26	-36	+40	101.6	Defervescence

6	62 86 88 82	.408 .418 .412 .406	19.0 20.0 15.5 19.0	+41 +65 +52 +35	37.0 13.0 17.0 20.0	+47 +17 +17 +31	56.0 32.0 32.0 39.0	+46 +47 +38 +31	+5 -18 -18 -30	-43 -43 -30	+39 +42 +32	97.9 101.0 101.7 100.6	Control Chill Flush Defervescence
7	65 107	.405 .400	20.0 24.0	-9 -5	17.0 14.0	+64 +140	29.0 16.0	+25 +40	+20	-45	+65	98 103.7	Control Chill
8	74 76 113 113	.390 .403 .416 .411	21.0 16.0 16.0 21.0	+51 +52 +51 +51	20.0 8.0 5.0 1.0	+53 -19 -90 -31	41.0 21.0 13.0 21.0	+51 +30 +36 +46	-23.8 -23.8	-49 -68 -49	+3 +53 +53	99.0 99.6 103.8 102.0	Control Early chill Flush Defervescence
Effect of Oxy- gen 8a	61 97 100 95	.400 .412 .412 .390	17.0 16.0 16.0 16.0	+50 +49 +53 +46	21.0 9.0 9.0 6.0	+59 -90 -76 +46	37.5 11.0 11.5 22.0	+59 +14 +15 +46	6 6 6	-71 -70 -41	+59 +64 +56	99.0 101.7 103.3 102.0	Control Late chill Flush Defervescence
9	75 107 125 105	.392 .408 .412 .397	8.0 11.0 4.0 10.5	+69 +75 +118 +48	35.0 11.0 11.0 16.0	+48 +20 +37 +30	43.0 21.0 14.0 25.5	+52 +49 +55 +38	+38 -50 +31	-51 -68 -41	+43 +67 +40	98.2 101.0 102.4 101.4	Control Chill Flush Defervescence
Effect of Oxy- gen 9a	70 98 100 75	.390 .413 .438 .407	7.0 6.0 4.0 11.5	+50 +36 +59 +45	46.0 18.0 25.0 26.0	+60 +35 +59 +42	53.0 23.0 29.0 38.0	+60 +35 +60 +45	-14 -43 +64	-57 -45 -28	+40 +43 +7	98.6 101.0 102.4 100.2	Control Chill Flush Late defervescence

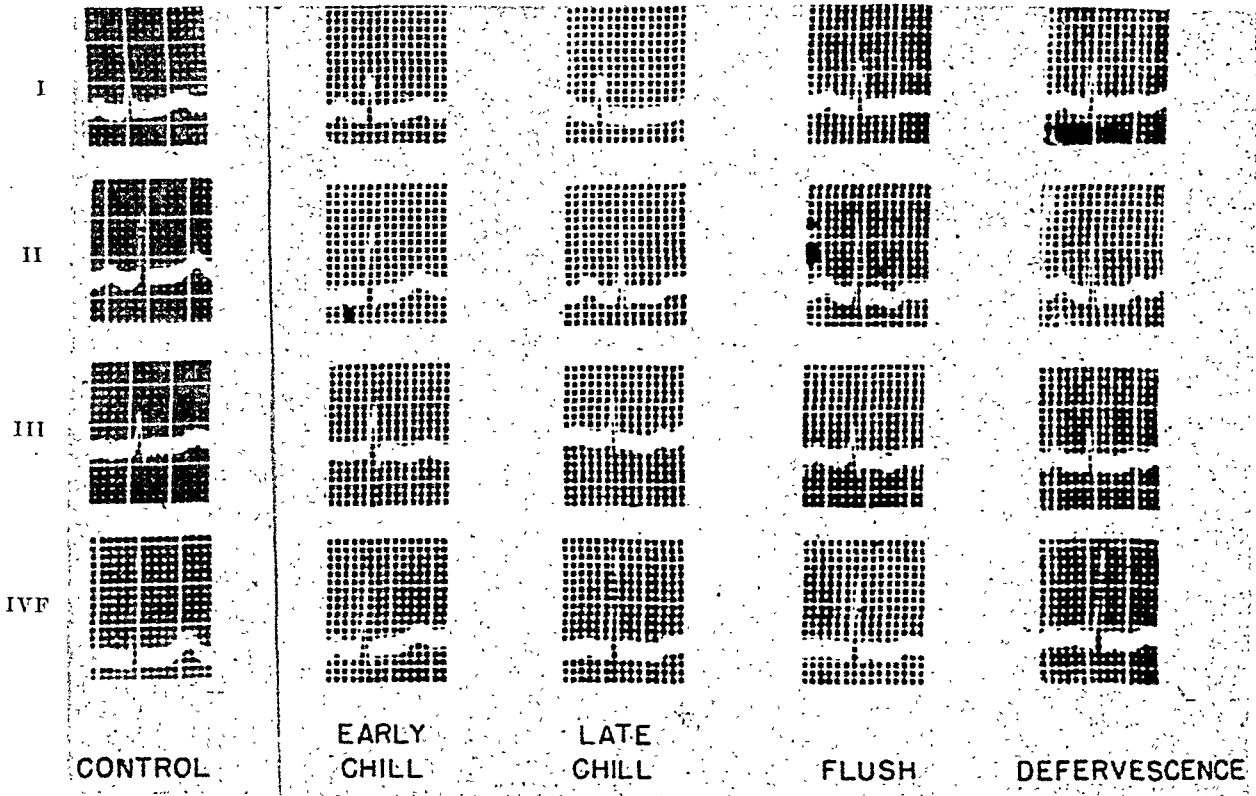


Fig. 5.—The electrocardiogram in Case 8 during the various phases of a febrile episode. T wave and S-T segment changes are present in the limb leads and Lead IVF in the chill and flush phases. A return toward the control is seen in defervescence.

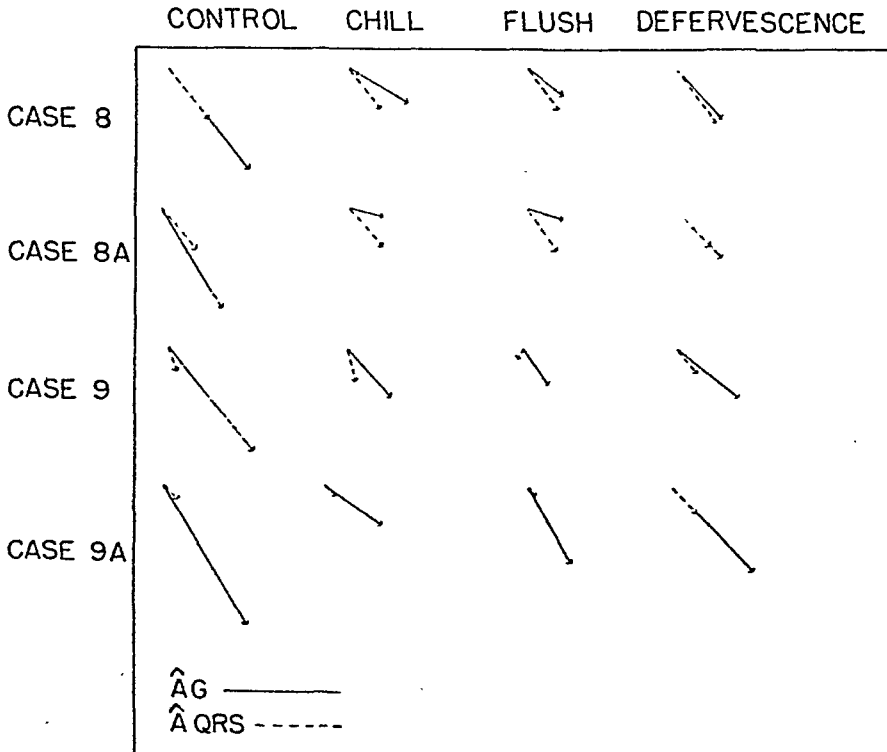


Fig. 6.—The effect of the administration of 100 per cent oxygen on the relation between $\hat{A}Qns$ and $\hat{A}G$.

in $\hat{A}T$ were present in the flush phase as compared with the chill phase. Marked alterations in the direction of $\hat{A}T$ occurred in the flush phase as compared to the chill in four instances (Table I). In all instances but one, $\hat{A}T$ increased during defervescence, represented in the electrocardiogram by an increase in the size of the T waves and/or a rise in the level of the S-T segment (Table I, Fig. 5).

$\hat{A}G$.—The control $\hat{A}G$ varied from 29 to 66 microvolt-seconds and $+25^\circ$ to $+61^\circ$. No change was observed in the prodrome. In the chill phase there was a decrease in $\hat{A}G$ in every instance, varying from 13 to 39 microvolt-seconds, and averaging 25.5, or 55 per cent. In the flush phase in seven cases there were no significant changes compared with the chill phase. When compared with the control, G was smaller by 18 to 43 microvolt-seconds (average 26.5 or 48 per cent). In Case 2 a return to the control value was observed. G was increased in six of the seven cases in defervescence as compared with the flush phase (Table I). In five instances it had not yet returned to the control values (Table I). Minor changes in direction during the chill were present in almost every instance. In one patient (Case 1) a marked rotation of approximately 70° to the left was present (Figs. 2 and 3, *C* and *D*). During the flush phase no additional significant shift was observed except in Case 1, in which return toward the control direction occurred (Figs. 2 and 3, *E*). During defervescence the direction of $\hat{A}G$ showed small rotational differences as compared with the control and flush phases.

The Effect of Oxygen.—In the two patients (Cases 8a and 9a) who were given oxygen continuously, the increase in the pulse rate was not as great as when oxygen was not administered. No differences in the values of K , $AQRS$, $\hat{A}T$ or $\hat{A}G$ were observed (Table I). The direction of $\hat{A}G$ in Case 8 during administration of

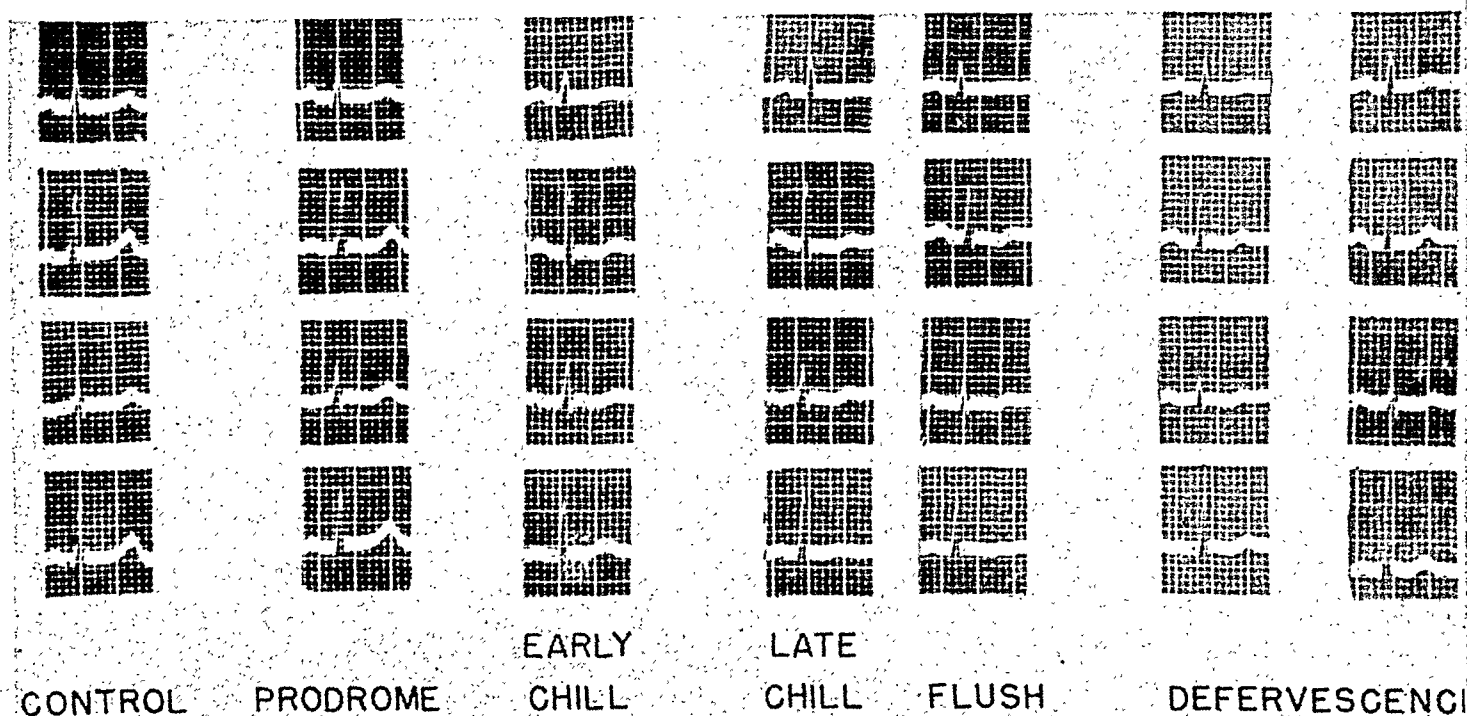


Fig. 7.—The electrocardiogram in Case 8a showing the effect of continuous oxygen administration during a febrile episode. This figure is to be compared with Fig. 5.

oxygen showed a more marked rotation to the right during the chill and flush phases (Fig. 6), and the electrocardiogram showed more marked T-wave inversion and S-T segment depression (Figs. 5 and 7).

COMMENT

The changes observed during fever include not only the effect of heating the heart but also the influence of concomitant physiologic factors,¹² such as cardiac rate, cardiac output, anoxia, hyperventilation, and accumulation of blood metabolites.

Cardiac Rate.—A 50 per cent increase in cardiac rate results in a decrease in G of approximately 39 per cent.^{15,16} It might be expected, therefore, that multiplication of net QRS-T area in microvolt-seconds by the cardiac rate per minute would show an increase in the size of G per minute. It is apparent that this does not occur (Table I). It is further clear that no correlation exists between the per cent increase in rate and the per cent decrease in G (Table I). Thus, in two instances (Cases 3 and 8) with a slight change in rate, a marked decrease in the size of AG occurred during the chill phase. Furthermore, shifts in the direction of $\hat{A}G$ should not occur with simple rate changes; such a shift was observed in Cases 1 and 8.

Cardiac Stroke and Minute Volume Output.—It has been suggested¹⁵ that changes in stroke output may cause a change in G and that an increased stroke volume is associated with a large gradient, and vice versa. Ashman¹⁶ attributed the increase in G during fever to increased stroke output. Previous studies,¹² however, have shown no striking changes in stroke output during fever induced by typhoid vaccine. Although the cardiac minute volume output may either rise or fall during the chill phase, it invariably increases markedly in the flush phase. If the changes in $\hat{A}G$ were related to minute volume output, they would be opposite in the chill and flush phases; it is apparent that this is not the case (Table I).

Hyperventilation.—The electrocardiographic changes observed in hyperventilation are characterized by inversion of T waves, and S-T segment depression.¹⁷ Calculation of the QRS and T-wave areas of electrocardiograms published in Thompson's paper¹⁷ is presented in Table II and Fig. 8 and shows that a de-

TABLE II. VENTRICULAR GRADIENT IN HYPERVENTILATION

	RATE	$\hat{A}QRS$		$\hat{A}G$		PER CENT INCREASE IN RATE	PER CENT INCREASE IN G
		M.V.S.	DEGREE	M.V.S.	DEGREE		
Control	77-60	41	-78	47	-75		
After hyperventilating	87	26.5	-72	25	-84	45	47

crease in the size of the gradient, assuming correct standardization, may occur after hyperventilation. In the leads used for the calculation, the control electrocardiogram shows a difference in rate of 77 and 60 beats per minute. The rate after hyperventilation is increased 45 per cent over the lower rate, while the gradient is decreased 47 per cent. There is a slight rotation of $\hat{A}G$ to the left, and a simultaneous slight shift of $\hat{A}QRS$ to the right. This change, therefore, is similar to those observed by us in some instances in fever (Table I, Fig. 2). Our previously published data¹² show that alkalosis occurs in the chill and flush phases and while alkalosis may be responsible for the changes in gradient observed, it may not be valid to make this interpretation since measurements of blood pH¹⁸ were not made simultaneously with recording of the electrocardiogram.

CONTROL AFTER HYPERVENTILATING

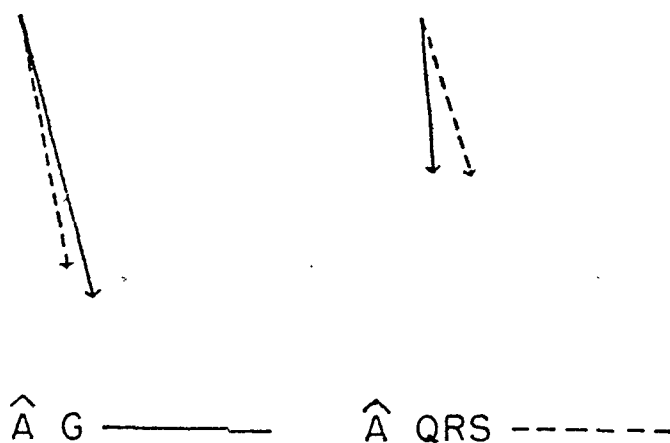


Fig. 8.—The relation between $\hat{A}QRS$ and $\hat{A}G$ in hyperventilation.

The value for K is most markedly increased in the flush phase suggesting that alkalosis is most severe at this time. The directional change in $\hat{A}G$, on the other hand, is less marked in the flush phase and in several instances $\hat{A}G$ returned to the control level in this phase while K was still increased (Table I). It is of interest that, recently in a group of patients with acute glomerulonephritis, La Due and Ashman¹⁹ found a rightward deviation of $\hat{A}G$ associated with decreased height and inverted T waves in Lead I and an increased height of the T wave in Lead III. In this group of patients the duration of the Q-T interval was longer than that observed when no gradient change was demonstrated.

Changes in the Myocardium Due to Local Effects of Heating.—In physically induced fever T-wave inversion and S-T segment changes occur.^{9,10,20} No analysis of the ventricular gradient under these circumstances has been found in the literature. It is apparent from the present study that the temperature within the myocardium cannot be an important factor in causing the observed changes, for the gradient returns toward the control in the flush phase (Cases 1, 2, and 3).

Anoxia.—In our previous studies no evidence of arterial oxygen unsaturation was noted in any phase of fever. A lowered venous oxygen content occurs in the chill phase but is not present in the flush phase. The persistence of the electrocardiographic changes in the flush phase would negate anoxia as the sole cause of these changes. Furthermore, a more marked shift in the ventricular gradient to the left occurred in Case 8 while oxygen was being administered.

Increase in Metabolites in Blood.—Unpublished data²¹ show progressive rises in blood pyruvate and lactate during the febrile episode. While it is not known whether similar increases in other tissue metabolites occur, it is clear that the observed changes in the ventricular gradient do not parallel the blood chemical changes.

Significance of the Observed Changes.—Analysis of the ventricular gradient affords a better understanding of the commonly observed T wave and S-T segment changes associated with fever. In approximately half of the cases, the occurrence of these changes is explained by a change in the position of the heart and/or an increased heart rate. In the remaining cases the T wave and S-T segment changes are primary, indicating physiologic alterations in the myocardium of unknown origin. The decreased magnitude of the gradient without change in its direction is not unlike that seen after digitalis administration,¹⁶ and is therefore not necessarily an indication of a deleterious change in the myocardium.

SUMMARY AND CONCLUSIONS

1. The electrocardiographic changes observed during fever induced by the intravenous injection of typhoid vaccine in man have been studied. The three standard limb leads and Lead IV F were recorded in the control, prodromal, chill, flush, and defervescent periods of the febrile reaction. The QRS and T-wave areas, the duration of electrical systole corrected for rate, and the P wave and P-R interval were studied.
2. No significant changes were observed during the prodrome.
3. The heart rate increased approximately ten beats per minute per degree Fahrenheit rise in body temperature. In three patients, at the onset of the chill phase, a slight to moderate decrease in the heart rate was observed.
4. No significant changes in the height or duration of the P wave, or in the P-R interval, were observed in any of the phases.
5. In eight of nine patients, an increase in K was observed in the chill and flush phases with a return toward the control value in defervescence. This may be attributed to alkalosis which occurs in fever.
6. The height of the T wave in Lead IVF decreased in the chill phase and remained so in the flush and defervescence phases.
7. In all patients a decrease in the magnitude of the ventricular gradient was observed in the chill phase. This was manifested in the electrocardiogram by a decreased height or inversion of the T wave and depression of the S-T segment. During the flush phase in two of nine patients partial return toward

the control values occurred, but in the remaining patients this did not occur until defervescence. There was no uniform change in direction of the ventricular gradient during any of the phases. Two instances of pronounced shift of $\hat{A}G$, one toward the left, the other toward the right, were observed. In the latter a more marked shift was observed while oxygen was being administered.

8. The decrease in the magnitude and the change in direction of $\hat{A}G$ without a corresponding change in $\hat{A}QRS$ in some cases are interpreted as signifying that the observed T wave and S-T segment changes in fever are primary. They denote the existence of definite but reversible changes in the myocardium of unknown origin and significance.

9. In the remaining cases the T wave and S-T segment changes can be explained by a change in the position of the heart and/or increased heart rate.

REFERENCES

1. Burnett, C. T., and Piltz, G. F.: The Electrocardiogram in Acute Infections, *J.A.M.A.* 93:1120, 1929.
2. Arjeff, M. J., and Tigi, R. R.: Elektrokardiographische Beobachtungen bei Typhus abdominalis, *Ztschr. f. klin. Med.* 112:641, 1930.
3. Master, A. M., Romanoff, A., and Jaffe, H.: Electrocardiographic Changes in Pneumonia, *AM. HEART J.* 6:696, 1931.
4. Tur, A.: Electrocardiographic Studies in Acute Diffuse Glomerulonephritis, *Klin. Med.* 13:1372, 1935.
5. Krinsky, L.: Beobachtungen über Elektrokardiographie bei Pneumonie, *Ztschr. f. klin. Med.* 128:27, 1935.
6. Weicker, B., and Kessler, M.: Impfmalaria und Herzstromkurve, *Ztschr. f. Kreislaufforsch.* 30:9, 1938.
7. Candel, S., and Wheelock, M. C.: Acute Nonspecific Myocarditis, *Ann. Int. Med.* 23:309, 1945.
8. Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis), *Arch. Int. Med.* 76:257, 1945.
9. Knies, P. T.: The Electrocardiogram in Induced Fever, *AM. HEART J.* 22:804, 1941.
10. Clagett, A. H., Jr.: Electrocardiographic Changes Following Artificial Hyperpyrexia, *Am. J. M. Sc.* 208:81, 1944.
11. Altschule, M. D., and Freedberg, A. S.: Circulation and Respiration in Fever, *Medicine* 24:403, 1945.
12. Altschule, M. D., Freedberg, A. S., and McManus, M. J.: Circulation and Respiration During an Episode of Chill and Fever in Man, *J. Clin. Investigation* 24:878, 1945.
13. Wilson, F. N., MacLeod, A. G., Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, *AM. HEART J.* 10:46, 1934.
14. Ashman, R., Byer, E., and Bayley, R. H.: The Normal Human Ventricular Gradient I. Factors Which Affect Its Direction and Its Relation to the Mean QRS Axis, *AM. HEART J.* 25:16, 1943.
15. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient II. Factors Which Affect Its Manifest Area and Its Relationship to the Manifest Area of the QRS Complex, *AM. HEART J.* 25:35, 1943.
16. Ashman, R.: The Genesis of the Electrocardiogram, *Mod. Concepts Cardiovascular Disease* 13:5, 1944.
17. Thompson, W. P.: The Electrocardiogram in the Hyperventilation Syndrome, *AM. HEART J.* 25:372, 1943.
18. Gertler, M. M., Hoff, H. E., and Humm, D. G.: The Acid Tolerance of the Dog's Heart, *Am. J. Physiol.* 146:478, 1946.
19. La Due, J. S., and Ashman, R.: Electrocardiographic Changes in Acute Glomerulonephritis, *AM. HEART J.* 31:685, 1946.
20. Harvey, A. M., and Billings, F. T.: Coronary Occlusion After Fever Therapy for Sulfamide-Resistant Gonorrheal Urethritis, *AM. HEART J.* 29:205, 1945.
21. Unpublished data.

Clinical Reports

SECONDARY HYPERTROPHIC OSTEOARTHROPATHY IN CONGENITAL HEART DISEASE

MYRON G. MEANS, M.D., AND N. WORTH BROWN, M.D.
TOLEDO, OHIO

SINCE the early descriptions of secondary osteoarthropathy by von Bamberger and by Marie, there have been numerous and divergent opinions as to its etiology. The role of chronic pulmonary diseases, including bronchiectasis, tuberculosis, empyema, abscess, malignancy, and other conditions producing extensive proliferation of interstitial tissue in the lungs, have been considered essential factors in its development. In this country, Thayer¹⁵ reported several cases of secondary pulmonary osteoarthropathy and differentiated its features from those of acromegaly. In 1903, Janeway⁷ reviewed the subject, adding cases of his own, and commented on the rarity of the condition. Landis⁹ described his findings in two cases associated with old tuberculous lesions and in his discussion stated that of 109 recognized cases only nine had been found in the United States. Brooks,³ in discussing the etiology of secondary osteoarthropathy, expressed his belief that long standing disease of the lungs was the principal cause. Kessell,⁸ in an investigation of thirty-two cases of pulmonary tuberculosis with clubbed fingers, found significant bone changes in ten of his patients. In a recent study of the circulation in clubbed fingers, Charr and Swenson⁴ reported six cases showing increased vascularity, but osteoarthropathy was not discussed. Five of their patients had chronic pulmonary disease, but one was a young man of 25 with a congenital cardiac defect and it is possible that a careful study of the long bones might have revealed some of the changes associated with osteoarthropathy.

In a comprehensive review of the subject in 1915, Locke¹⁰ analyzed 144 cases and ascribed six to heart disease but only two to congenital lesions. In addition to the original case described by von Bamberger, there has been reported the well-authenticated case of Shaw and Cooper¹³ in a patient with congenital heart disease, and another by Thorburn¹⁶ in a patient with a valvular defect of uncertain origin.

It is significant that by far the greater number of reported cases of osteoarthropathy have occurred in connection with pulmonary lesions, whereas the only successful reproduction of the characteristic bone lesions in animals was secured by Mendlowitz and Leslie¹² who established an artificial communication between the pulmonary artery and the left auricle in a dog, duplicating as nearly as possible the oxygen unsaturation present in congenital malformations of the heart with cyanosis. An autopsy eight months later showed the changes typical of hypertrophic osteoarthropathy.

The case which we describe gives no history, physical signs, nor roentgenologic signs of pulmonary disease, but presents the classical picture of the tetralogy of Fallot, with cyanosis, polycythemia, bulbous fingers and toes, soft tissue deformities about the wrists and ankles, and roentgenologic evidence of a hypertrophic osteoarthropathy.

CLINICAL REPORT

L. S., 26 years of age, a bookkeeper, was born a "blue baby," and had been cyanotic during his entire life. There is no history of heart trouble or of any congenital defects in his family. His childhood was uneventful and he escaped the usual childhood diseases. Deformities of the wrists and ankles were first noticed at the age of 12 years. During adolescence he had periodic pain in the wrists and ankles and at the age of 15 years he had an attack of "flu"; at no other time were these joint pains accompanied by fever. He completed a high school education, but was not able to engage in any occupation or recreation which required physical exertion.

The patient was first examined at the Toledo Clinic in January, 1946. There was a moderate general cyanosis which was most conspicuous in the hands and feet. The fingers and toes showed marked clubbing and there were soft irregular swellings about the wrists and ankles (Figs. 1 and 2). The hands presented the clawlike appearance mentioned by early writers. The lower legs suggested the "elephant foot" described by von Bamberger in one of his cases. There was no tenderness to pressure nor was there pain on manipulation of the joints. Finger- and toenails were unusually broad in proportion to the width of the digits. There were patches of dark purple discoloration on the lower extremities. Body development was normal. There was nothing to indicate acromegaly. The chest was of normal shape and expansion was equal. The respiratory sounds were normal and there were no findings which indicated any chronic pulmonary disease. The heart was not appreciably enlarged, but the width of manubrial dullness was increased. On palpation a double systolic impulse was felt over the precordium and was visible in the vessels of the neck. On auscultation a loud systolic murmur was heard, maximum in the fourth and fifth intercostal spaces to the left of the sternum. This murmur was transmitted to the right rather than to the left. Another systolic murmur of higher pitch and different quality could be heard in the second left intercostal space, but was not accompanied by the thrill usually found in pulmonary stenosis. No diastolic murmurs could be discovered. The second sound was louder to the left than to the right of the sternum. The pulse was of regular rhythm with a rate of 88 per minute. The brachial pressure was 124/86, and the systolic pressure in the lower extremity was 140 by palpation.

There was a compensatory polycythemia with an erythrocyte count of 7,260,000 and a hemoglobin reading of over 140 per cent. The leucocytes numbered 6,550 with a normal differential count. The sedimentation rate was normal. Kahn and Wassermann tests were negative.

The electrocardiogram (Fig. 3) showed a normal sinus rhythm and a rate of 84 per minute. The P-R interval measured 0.20 second; the QRS interval, 0.08 second. There was a definite right ventricular preponderance. The auricular complexes were unusually high in Leads I and II. Special unipolar parasternal leads showed large diphasic auricular waves in the second, third, and fourth intercostal spaces to the right of the sternum. The character of auricular waves of

this type showing an abrupt intrinsic deflection suggested the proximity of the auricular wall to the parasternal electrodes, and located the right auricle somewhat to the right and above its usual position.

The clinical diagnosis, based on the history, physical examination, and electrocardiographic findings, was that of congenital heart disease of the Fallot type.

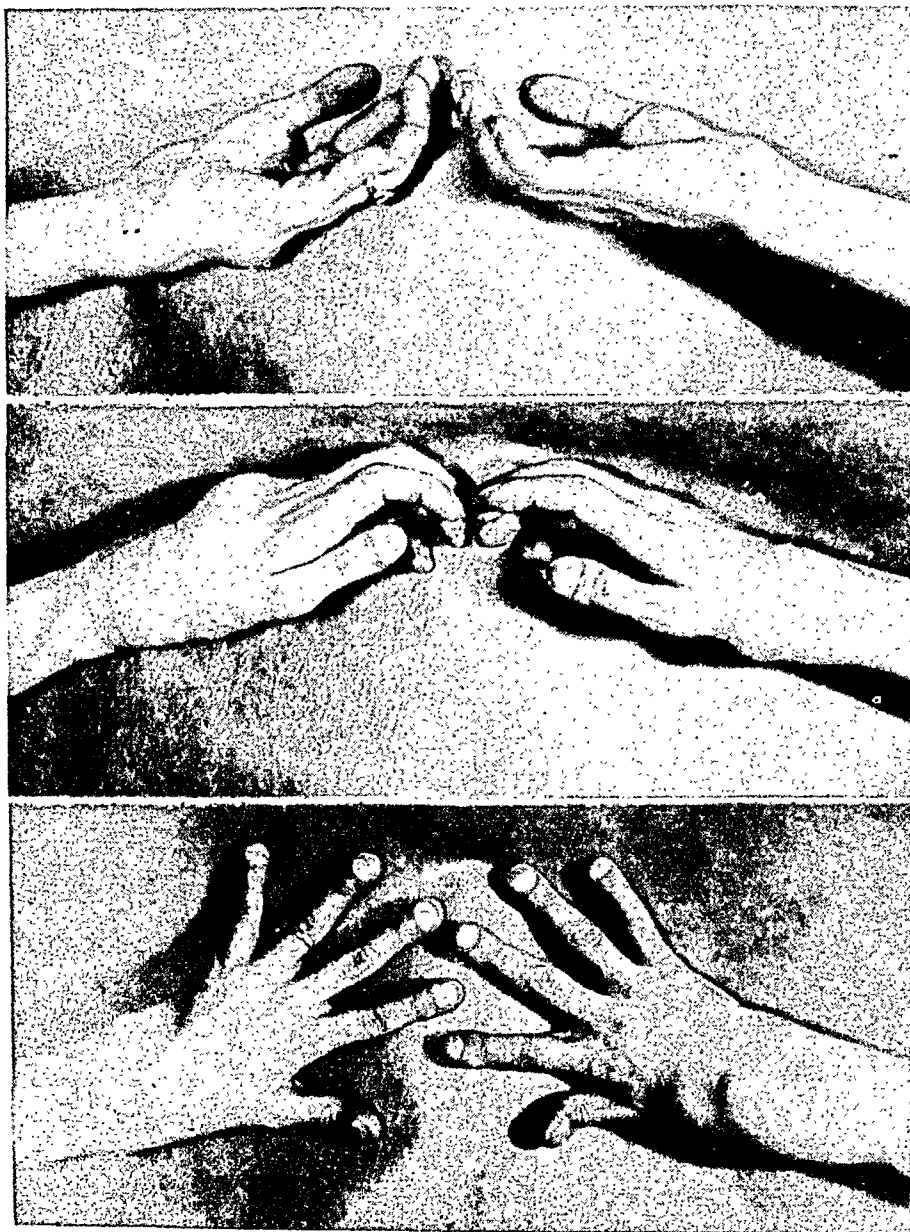


Fig. 1.—Dorsal and lateral views of the hands, showing the clubbed fingers, broad arched finger-nails, deep cyanosis of the finger tips, the spindleshaped joints, the irregular swellings over the carpals and metacarpals, and the clawlike position of the fingers.



Fig. 2.—Lower extremities, showing clubbing of the toes, irregular swellings about the ankles, cyanotic areas on the feet, and the diffuse exanthematous rash on the lower anterior portion of the leg.

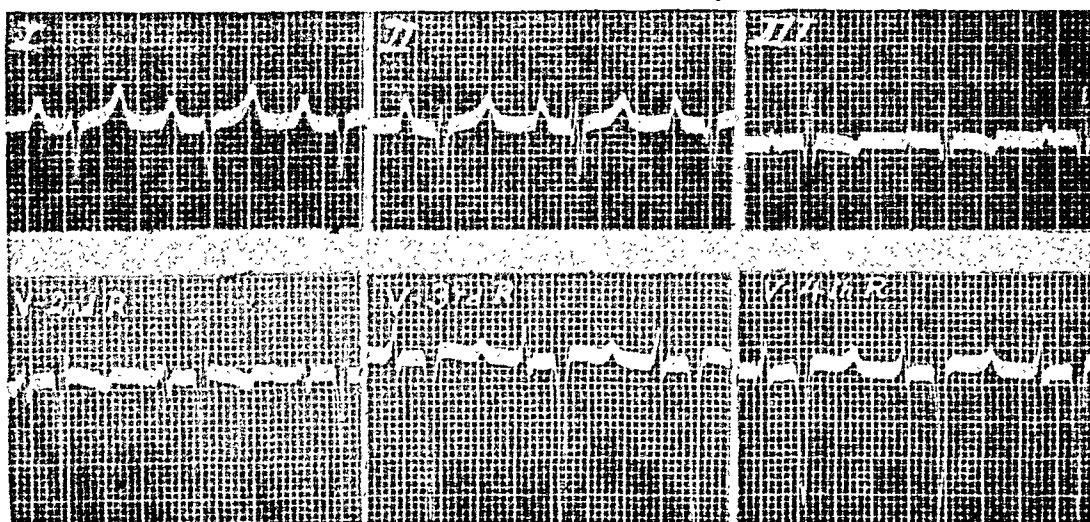


Fig. 3.—Upper: Standard leads. Right ventricular preponderance. Unusually large auricular waves in Leads I and II.

Lower: Unipolar parasternal leads from the second, third and fourth intercostal spaces to the right of the sternum show the abrupt intrinsic deflection in the P waves characteristic of direct leads from the auricular wall. The presence of these waves suggests the juxtaposition of the right auricle with the chest wall directly beneath the exploring electrode. Intrinsic deflections were not found to the left of the sternum.

Roentgenologic Discussion.—In the case under consideration, it is noteworthy that our roentgenograms failed to disclose any evidence of the usually purported etiological diseases of the pleura, lungs, mediastinum, or spine to account for the osseous and soft tissue changes in the extremities. Recognition of this fact immediately places this patient in a category of unusual interest; that of hypertrophic osteoarthropathy in uncomplicated congenital heart disease.

In the frontal plane view (Fig. 4) the cardiac silhouette does not appear to be definitely enlarged, although its area, when calculated according to the method of Hodges and Eyster,⁶ yields a 14 per cent increase over that predicted. The often described characteristic "coeur en sabot" configuration of right ventricular hypertrophy is somewhat modified by submergence of a portion of the heart shadow below that of the diaphragm. At the screen with the patient turned to the left oblique position an impression of right ventricular enlargement is obtained. Moreover, the right cardiac contour is rather prominent, suggesting a lateral displacement of the right auricle by hypertrophy of the right ventricle.

Of diagnostic significance is the complete absence of all signs pointing to enlargement of the outflow tract of the right ventricle. In addition to the slight reduction of the normal "waistline," the aortic window, as viewed in the left anterior oblique position, is easily recognized (Fig. 5).

By far the most conspicuous feature is the prominence of the right vascular contour which fluoroscopically shows an increased amplitude of pulsation. The aortic knob shows a synchronous thrust. In Fig. 5, the ascending and transverse aortic shadow appears large. This observation is in keeping with the enlargement of the ascending aorta described by White and Sprague¹⁷ in autopsy protocols of adults with the tetralogy of Fallot. Only as the hemodynamics are altered by it does the dextroposed aortic orifice itself participate in these morphologic changes.

Somewhat contrary to the concept of pulmonary circulatory deficiency in the tetralogy of Fallot, as expressed by Blalock and Taussig¹ and reflected in roentgenograms by the absence of prominent vascular markings, this patient does show evidence of increased lung vascularity. The changes are most pronounced in the peripheral zone of the lungs. The hilar shadows are also prominent, and upon close inspection and analysis disclose an unusual number of component parts.

In view of our patient's age and the absence of abnormal pulsations in the hilar vessels, coupled with the lack of other evidence of a patent ductus arteriosus, we believe these changes in the pulmonary circulation are largely secondary to the polycythemia and its concomitant increased plasma volume, operating over a long period of time and producing an ectasia of the pulmonary blood vessels. Another consideration which cannot be eliminated is the possible development of a collateral circulation between the systemic and the pulmonary circulations through small blood vessels, particularly in the hilar area.

The roentgenograms of the extremities (Figs. 6 and 7) disclose symmetrical hypertrophy of the radii, ulnae, tibiae, and fibulae. The broadening of these bones is in sharp contrast to the relatively normal diameter of the carpus and tarsus and the more distal bones of the hands and feet. The radii and ulnae



Fig. 4.—Roentgenograms of the chest. *A*, Frontal view shows a relatively narrow "waist" in contrast to the convexity seen in other congenital defects and acquired lesions. *B*, Lateral view shows an adequate retrocardiac space and an increase in the hilar shadows.

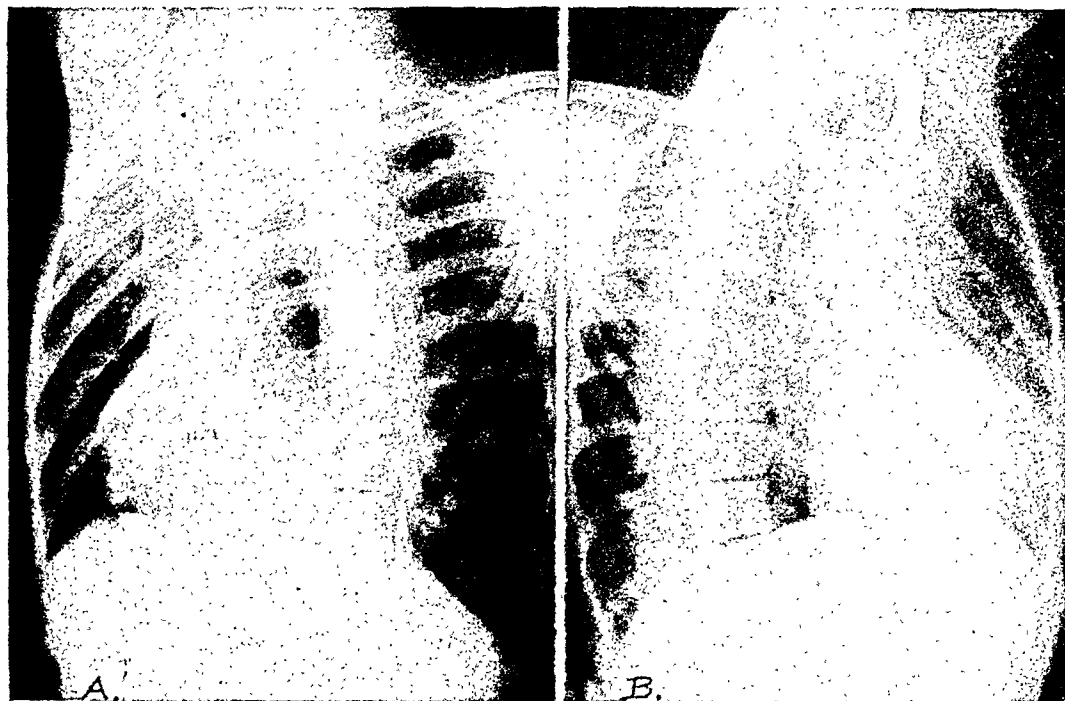


Fig. 5.—Roentgenograms of the chest. *A*, Left oblique view shows unusual clarity of the "aortic window." *B*, Right oblique view shows preservation of the retrosternal triangular space and a rather large ascending aorta.

show a well-differentiated cortex with only a slight roughening along the interosseous margins of the former. The lower tibia (Fig. 7), however, displays a very definite delineation between the ossifying periosteal new bone formation and a well-organized underlying cortex. At several points of tendon and ligament

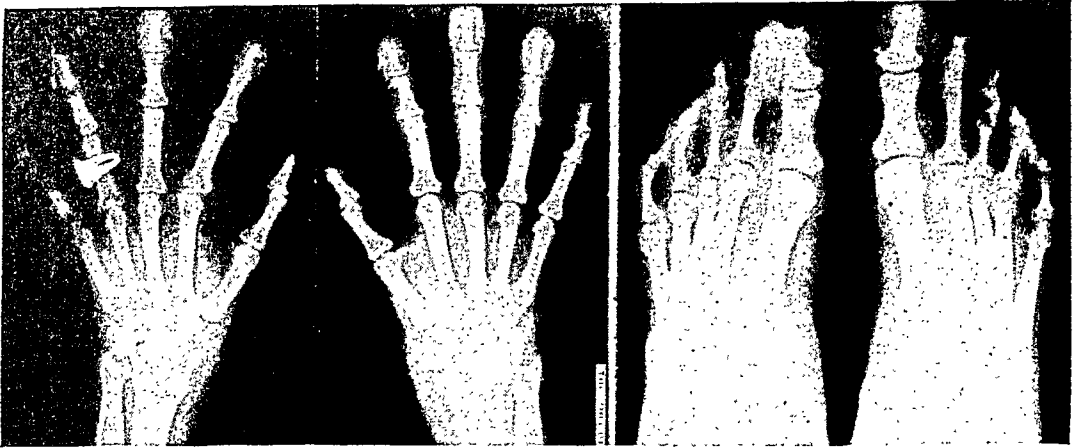


Fig. 6.—Roentgenograms of the hands and feet present an interesting contrast between the terminal phalanges of the feet and those of the hands. The distal portions of the radius and ulna show an increased diameter. Soft tissue hyperplasia is evident.



Fig. 7.—Roentgenograms of the lower legs show thickening of the tibial and fibular diaphyses and residual productive periosteal changes in the distal portion of the long bones.

insertion, notably at the radial styloids, the external tibial tuberosities, and the internal malleoli, there are osteophytic irregularities as well as hypertrophy.

A striking feature is the soft tissue hyperplasia of the wrists and ankle joints (Figs. 1 and 2), the production of which probably depends on the same factors which cause proliferation of the cambium layer of the periosteum. The soft

tissues about the terminal phalanges of all fingers and toes show the bulbous enlargement characteristic of clubbing. The tufted portion of the terminal phalanges of the fingers appears smooth, whereas that of the toes shows well-advanced bone resorption with a resulting sharpening and spinelike pointing of the tips (Fig. 6). This discrepancy between the upper and lower extremities suggests the possibility of a hypostatic etiological factor and supports the theory that an altered blood flow is at least an important adjunct, if not the primary cause. It is to be noted that similar osseous changes are found in Raynaud's and Buerger's diseases. Inferior to the external malleolus and anterior to the ankle joint there can be seen several circumscribed areas of finely granular density, which indicates a deposition of calcium salts in the thickened soft tissues which lie adjacent to and perhaps involve the joint capsules. No phleboliths or other signs suggesting angiomatous formations were found and no destruction of the articular cartilages could be demonstrated.

Subsequent Record.—On May 6 an anastomosis was established between the right common carotid and the right pulmonary arteries.* Notwithstanding the patient's age the result was satisfactory. Dyspnea was relieved and cyanosis could be recognized only on critical inspection. During the operation it was necessary to resect the right subclavian artery. Collateral blood vessels maintained an adequate circulation in the right arm. It was of particular interest to find that within six weeks the deformities about the hands and feet had become less conspicuous. The change was especially noticeable in the right hand which had lost its grotesque appearance and was almost normal in size and shape. Another finding of significance was the evidence, in chest films and by fluoroscopic examination, of the persistence of a vascular increase in the right lung, while the left lung appeared relatively normal. The erythrocyte count had fallen to 6,000,000 and the hemoglobin to 120 per cent. It was estimated by Taussig¹⁴ that oxygenation of the blood was doubled by the carotid-pulmonary anastomosis. Our recent examination indicates that this increase in pulmonary circulation is preponderantly within the right lung.

COMMENTS

The presence of large, soft, irregular swellings about the wrists and ankles, as illustrated in Figs. 1 and 2, gives rise to speculation as to their connection with the proliferative changes in the bones and periosteum. Thayer¹⁵ describes similar conditions in his report on secondary pulmonary osteoarthropathy and states: "Effusions into the joints are common, the joints most commonly affected being those nearest the bony changes, as the ankle, wrist and elbow. Enlargement of the lower part of the forearm accompanies the changes in the hands. . . . In some cases the enlargement is due entirely to hypertrophy of the soft tissues. Analogous changes take place in the feet and legs." Janeway⁷ in his description of the findings in a man, 22 years of age, with chronic suppurative bronchiectasis and secondary osteoarthropathy, states that "One was struck with the tremendous size of the hands and feet . . . the lower third of leg and arm were much enlarged so that both had a straight line from knee and elbow to ankle and wrist." Thorburn¹⁶ also mentions "Excessive fluid in the joints and some erosion of the cartilages." The illustrations attached to the descriptions by Thayer and Janeway present a striking resemblance to those of the case

*By Dr. A. Blalock, Baltimore, Md.

which we present. Wissing and Weisz¹⁸ discovered progressive hypertrophic bone changes in a dog with pulmonary carcinomatosis. Soft tissue swellings were noted on both fore and hind legs. Autopsy showed the bone lesions and the periosteal proliferation of secondary osteoarthropathy and also considerable hyperplasia of the connective tissues.

It has been suggested that these soft tissue deformities about the ankles and wrists should be regarded as due to independent, coexisting congenital defects in the tendon sheaths or to congenital cystic hygromata. In view of the fact that deformities of this character have been so frequently reported in the secondary osteoarthropathy of acquired pulmonary disorders, it seems unnecessary to assume the presence of additional, unrelated congenital defects. It is more reasonable to consider them as associated with the proliferative and degenerative changes in the bones and periosteum and due to the same etiological factors. It is significant that these soft tissue deformities are in close proximity to the bone lesions and are not found in other localities. As with osteoarthropathy they are found in the most dependent portions of the extremities which in itself points to the influence of peripheral stasis.

The postoperative changes in the soft tissues of the extremities show that some of the conditions associated with secondary osteoarthropathy are reversible and lend support to the view that the dynamics of the circulation have a part in producing the soft tissue deformities. The fact that local improvement was most marked in the arm which had been deprived of its normal blood supply furnishes additional evidence that increased vascularity and peripheral stasis contribute to the soft tissue hyperplasia and probably also to the characteristic changes of secondary osteoarthropathy.

That these changes are most commonly associated with chronic pulmonary disease is evident from the analytical reports of Locke¹⁰ and a more recent review of the entire subject by Mendlowitz,¹¹ and yet the occasional but well-proven cases of secondary hypertrophic osteoarthropathy developing late in the cyanotic group of patients with congenital cardiac defects must be conceded.

In view of the perfection of surgical procedures as developed by Gross⁵ and Blalock and Taussig^{1,2} it becomes of increasing importance for the clinician and the roentgenologist to recognize and identify the cardiac malformations amenable to early surgical treatment.

SUMMARY

A case of secondary hypertrophic osteoarthropathy associated with uncomplicated congenital heart disease of the Fallot type is presented, together with a roentgenologic study and with illustrations showing the gross physical deformities, electrocardiographic records, and x-ray findings. The etiology is discussed and evidence is given to show that increased vascularity and peripheral stasis are important contributing factors in the production of connective tissue hyperplasia, as well as of characteristic changes in bone and periosteum.

REFERENCES

1. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, *J. A. M. A.* 128:189, 1945.
2. Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects, *Bull. New York Acad. Med.* 22:57, 1946.
3. Brooks, H.: Etiology of Hypertrophic Pulmonary Osteoarthropathy, *New York, M. J.* 98:608, 1913.
4. Charr, R., and Swenson, R. C.: Clubbed Fingers, *Am. J. Roentgenol.* 55:325, 1946.
5. Gross, R. E.: Complete Surgical Division of Patent Ductus Arteriosus, *Surg., Gynec. & Obst.* 78:36, 1944.
6. Hodges, P. C., and Eyster, J. A. E.: Estimation of the Cardiac Area in Man, *Am. J. Roentgenol.* 12:252, 1934.
7. Janeway, T. C.: Hypertrophic Osteoarthropathy With Report of Two Cases, *Am. J. M. Sc.* 126:563, 1903.
8. Kessell, L.: Relation of Hypertrophic Osteoarthropathy to Pulmonary Tuberculosis, *Arch. Int. Med.* 19: 239, 1917.
9. Landis, H. R. M.: Hypertrophic Pulmonary Osteoarthropathy, *Pennsylvania M. J.* 10: 852, 1907.
10. Locke, E. A.: Secondary Hypertrophic Osteoarthropathy and Its Relation to Simple Club-Fingers, *Arch. Int. Med.* 15:659, 1915.
11. Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy, *Medicine*, 21:269, 1942.
12. Mendlowitz, M., and Leslie, A.: Experimental Stimulation in the Dog of the Cyanosis and Hypertrophic Osteoarthropathy Which Are Associated With Congenital Heart Disease, *AM. HEART J.* 24:141, 1942.
13. Shaw, H. B., and Cooper, R. H.: Pulmonary Hypertrophic Osteoarthropathy in a Case of Congenital Heart Disease, *Lancet* 1:880, 1907.
14. Taussig, Helen B.: Personal communication.
15. Thayer, W. S.: Hypertrophic Pulmonary Osteoarthropathy and Acromegaly, *Phila. Med. Jour.* 2:955, 1898.
16. Thorburn, W.: Three Cases of Hypertrophic Pulmonary Osteoarthropathy, *Brit. M. J.* 1:1155, 1893.
17. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot, *J. A. M. A.* 92:787, 1934.
18. Wissing, E. G., and Weisz, L.: Pulmonary Osteoarthropathy in a Dog, *Am. J. Roentgenol.* 50:527, 1943.

ELECTROCARDIOGRAPHIC CHANGES RESULTING FROM ACUTE COCAINE INTOXICATION

DENNISON YOUNG, M.D., NEW YORK, N. Y., AND
JÉROME J. GLAUBER, M.D.
BUFFALO, N. Y.

BECAUSE of the urgency of the situation and the frequent rapid demise of the patient, electrocardiographic observations during acute cocaine poisoning have not been reported. Although several investigators¹⁻⁴ have recorded graphically the effects of the cocaine group of drugs applied upon or injected into the hearts of experimental animals, search of the literature fails to reveal electrocardiograms obtained during the course of clinical cocaine or novocaine reactions. The following study is presented because a unique opportunity arose for clinical observation over a five and one-half hour period before the patient succumbed to acute cocaine intoxication.

REPORT OF CASE

A 20-year-old white man was admitted to the hospital for the purpose of a nasal submucous resection. The past history revealed no serious illnesses or previous operative procedures. Examination showed a moderately severe deviation of the nasal septum to the right. The heart was not enlarged, the sounds were of good quality, the rhythm was regular at a rate of 80 per minute, and there were no murmurs. The blood pressure was 108/66. The lungs and abdomen revealed no abnormalities. All laboratory data were normal.

The night before operation the patient received $1\frac{1}{2}$ grains of nembutal. The following morning breakfast was withheld and at 9:00 A.M., $\frac{1}{4}$ grain of morphine sulfate and 1/100 grain of atropine sulfate were administered hypodermically. At 9:30 A.M., $1\frac{1}{2}$ grains of nembutal were given by mouth. On arrival at the operating room the patient was in excellent condition and fully conscious. At 10:15 A.M., preparation for nasal surgery was begun. This consisted of intermittent spraying of small amounts of a solution of 20 per cent cocaine containing ten minims per ounce of 1/1000 epinephrine. Approximately 6.0 c.c. of this topical spray were used over a period of fifteen minutes. A large incalculable amount of the solution was either forcibly expelled from the nose or drawn into the nasopharynx and expectorated by the patient, so that only a small amount of the solution used actually remained in contact with the nasal mucosa.

At 10:35 A.M., about five minutes after completion of the anesthetization, the patient complained of sudden nausea which lasted for about two minutes. At this time it was noted that he was becoming restless and incoherent in speech, the eyes showed a "far-away" distant stare, and facial grimacing occurred. The head of the table was lowered, and by the time the patient was in a recumbent position there was intense tonic spasm of the arms and legs followed by extreme rigidity with the entire body in the opisthotonos position. Apnea and unconsciousness were immediate. Artificial respiration and oxygen by face mask were administered. The tonic spasm ceased shortly and was followed by short convulsive clonic spasms of the arms and legs and

rapid shallow respirations. Also noted was a dead white pallor of the lower extremities. The dorsalis pedis pulsations were not obtained; the posterior tibial pulsations were moderate and of equal intensity.

Approximately ten minutes after the onset of the initial reaction, $7\frac{1}{2}$ grains of sodium amytal were administered intravenously and complete subsidence of the convulsive movements occurred. At this time examination of the heart revealed a mid-diastolic gallop rhythm that was regular and at a rate of 150 per minute. The blood pressure was 140/50-0. Subsequently, the heart showed a varying arrhythmia with multiple premature contractions with compensatory pauses and runs of ectopic beats. At times there was a return to a regular rhythm at a rate of 165 per minute, the gallop persisting. At 11:00 A.M., the blood pressure was 100/50. At this time the first electrocardiogram was taken (Fig. 1).

At 11:10 A.M., the face mask was removed and an intranasal catheter was inserted. Oxygen was administered at a rate of five liters per minute for the duration of the patient's illness. A pharyngeal airway was inserted after respiratory difficulty was experienced due to relaxation of the tongue. He remained unconscious and exhibited no further convulsive phenomena until 11:45 A.M., at which time slight clonic spasms of the arms, legs, and head occurred. These were

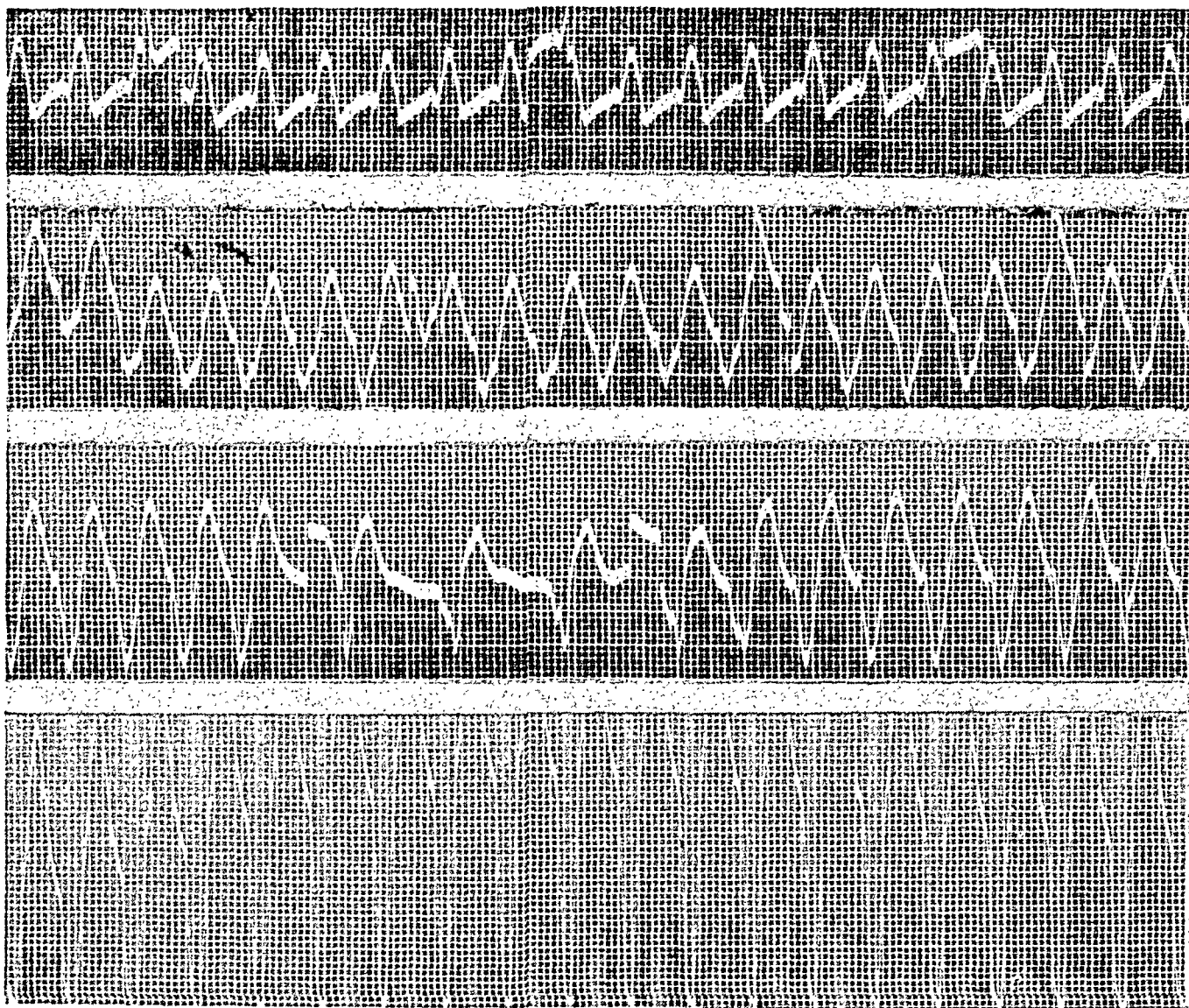


Fig. 1.—Initial tracing twenty-five minutes after onset of cocaine reaction. Ventricular tachycardia at a rate of 167 per minute is present. In Lead III there are three sinus beats with a P-R interval of 0.32 second. Ventricular conduction in these sinus beats is also aberrant.

immediately controlled by administration of $3\frac{3}{4}$ grains of sodium amytal intravenously. At this time it was noted that the pupils, which had previously been small due to the preoperative morphine, slowly and irregularly dilated. The corneal reflexes remained absent. The intense pallor of the lower extremities gradually diminished, although the dorsalis pedis pulsations did not become obtainable until approximately three and one-half hours after the initial event. An absence of sweating over the entire body during the early acute phase was also observed. This was accompanied by an axillary temperature of 101.2° Fahrenheit.

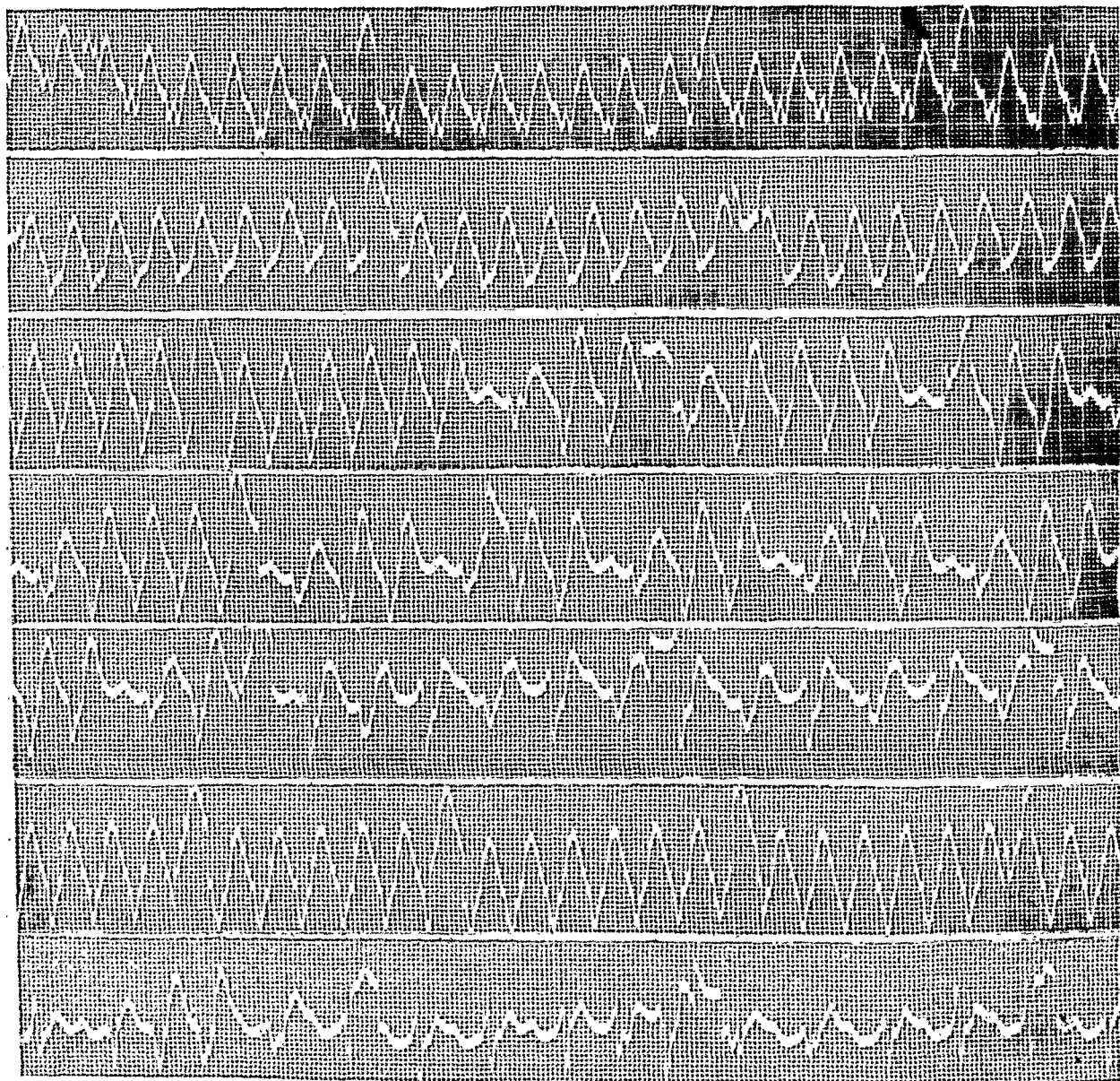


Fig. 2.—Continuous Lead II. In A and B ventricular tachycardia at a rate of 167 per minute is still present; C shows initial quinine effect. In C and D a basic sinus rhythm at a rate of 42 per minute has been established; runs of ventricular tachycardia occur between the sinus beats; the P-R interval measures 0.25 second. In E partial A-V dissociation has occurred; the auricular rate is 110 per minute; alternate auricular beats are conducted with a P-R interval of 0.24 second, giving a basic rate of 55 per minute. A parasystolic rhythm is present also at a rate of 55 per minute. In F the ventricular tachycardia at a rate of 167 per minute is re-established. In G a regular sinus rhythm at a rate of 100 per minute is present; the P-R interval measures 0.30 second; the form of the ventricular response varies.

Because of the persistence of ventricular tachycardia, at 11:52 A.M. intravenous quinine dihydrochloride (one gram per 100 c.c. of distilled water) was started and a continuous intravenous drip of this solution was maintained to a total of six grams up to 2:00 P.M. During this period the apical rate became slower and irregular. At times runs of tachycardia were observed, but more often multiple ectopic beats, frequently resulting in a bigeminal and trigeminal rhythm, were present (Figs. 2 and 3). The blood pressure varied from 106/60 to 130/70.

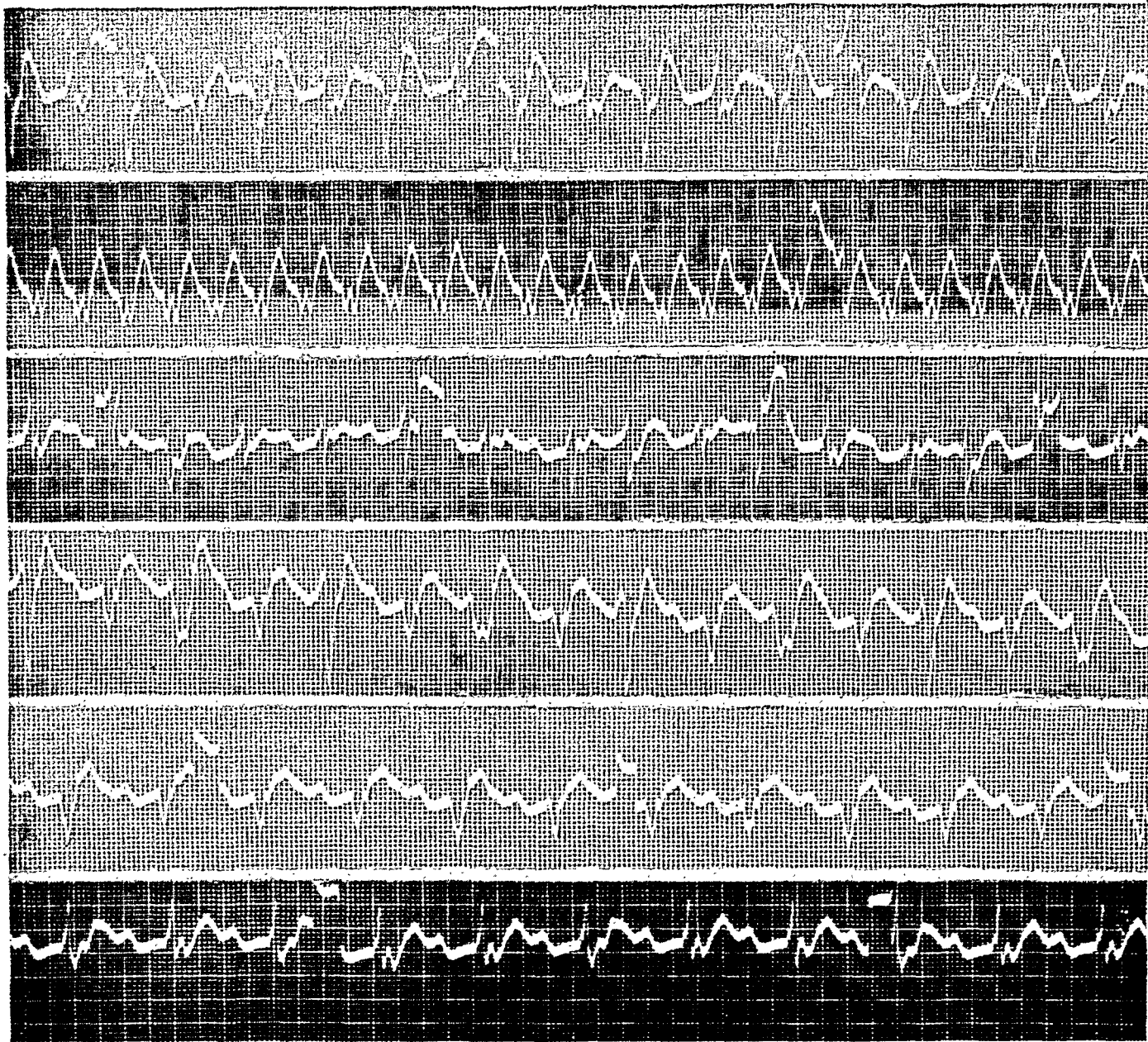


Fig. 3.—Continuous Lead II. In A there is total A-V dissociation with a bidirectional ventricular tachycardia at a rate of 115 per minute. In B the previous type of ventricular tachycardia is again present. In C a partial A-V dissociation with ectopic ventricular beats has occurred; the auricular rate is 167 per minute. In D the auricular rate is 100 per minute; alternate auricular beats are conducted with a P-R interval of 0.28 second and give a basic sinus rhythm of 50 per minute. Alternating between each of these sinus beats are two different ectopic ventricular foci, resulting in two parasystolic rhythms each at a rate of 25 per minute. In E a regular sinus rhythm at a rate of 75 is present; the P-R interval is 0.34 second; the QRS complex measures 0.12 second. In F a 2:1 A-V block is present; the auricular rate is 150 per minute, the ventricular rate, 75 per minute.

At 2:00 P.M. the patient reacted to the extent of expelling the pharyngeal airway and coughing out a small bloody mucous plug. This was not accompanied by consciousness nor by convulsive manifestations. Shortly thereafter, for the first time since the onset of the acute episode, the apical rhythm became regular at a rate of 75 per minute (Fig. 3,E). The quinine dihydrochloride was then discontinued. Ten to fifteen minutes later the regular rhythm and slow rate were no longer present. Multiple ectopic beats were again observed and because of this the quinine dihydrochloride intravenous drip was again started. During the subsequent two hours another two and one-half grams of the drug were given.

Never again was there a restoration of the sinus rhythm, although the heart rate was slower than previously and the gallop rhythm was no longer noted (Figs. 4 and 5). The patient remained comatose. The axillary temperature was 101° Fahrenheit. Mild diaphoresis occurred, notably over the face and neck. There was never any clinical evidence of congestive heart failure. Suddenly at 4:02 P.M., a short convulsive seizure occurred, during which the patient's head became extended and breathing ceased although the heart continued to beat. Artificial respiration and the usual heroic measures were of no avail and the patient was pronounced dead at 4:07 P.M., five and one-half hours after the onset of the initial cocaine reaction.

At *post-mortem examination* the only abnormal findings were moderate passive congestion of the left lower lobe of the lung, the liver, and the spleen.

DISCUSSION

Circulatory changes due to cocaine intoxication may result either from an overdosage of the drug or from individual susceptibility. Small doses may decrease the heart rate by central vagal action while moderate doses result in an acceleration of the rate due to sympathetic stimulation. Large doses intravenously may cause immediate death from cardiac failure due to direct toxic action on the heart.⁵ Reactions due to hypersensitivity, however, whatever may be the underlying mechanism, are completely independent of the dosage, and death has been reported from as little as 20 mg. of the drug.⁵

That the reaction in this patient was due to the cocaine seems quite certain because of the classical picture of acute cocaine poisoning presented. It is exceedingly unlikely that the small amount of epinephrine in the solution was responsible, for even if absorption of the entire 6.0 c.c. of solution sprayed had occurred, only 2 minims of epinephrine would have been absorbed with it. Because of the undoubtedly small amount of cocaine absorbed it is reasonable to assume that the reaction occurred because of an unusual degree of hypersensitivity to the drug. The circulatory effects are believed to have been of reflex central and peripheral origin, and were of two types:

1. *Vasoconstrictor*, manifested by the intense pallor of the lower extremities, absent dorsalis pedis pulsations, anhidrosis, hyperpyrexia, and transient mild rise in systolic blood pressure.
2. *Cardio-accelerator*, due to reflex central and peripheral sympathetic stimulation and manifested by the demonstrated electrocardiographic changes (Figs. 1-5).

The initial electrocardiogram was taken twenty-five minutes after the onset of the cocaine reaction, and frequent repeated tracings were recorded thereafter for the subsequent five hours. A ventricular tachycardia was present on

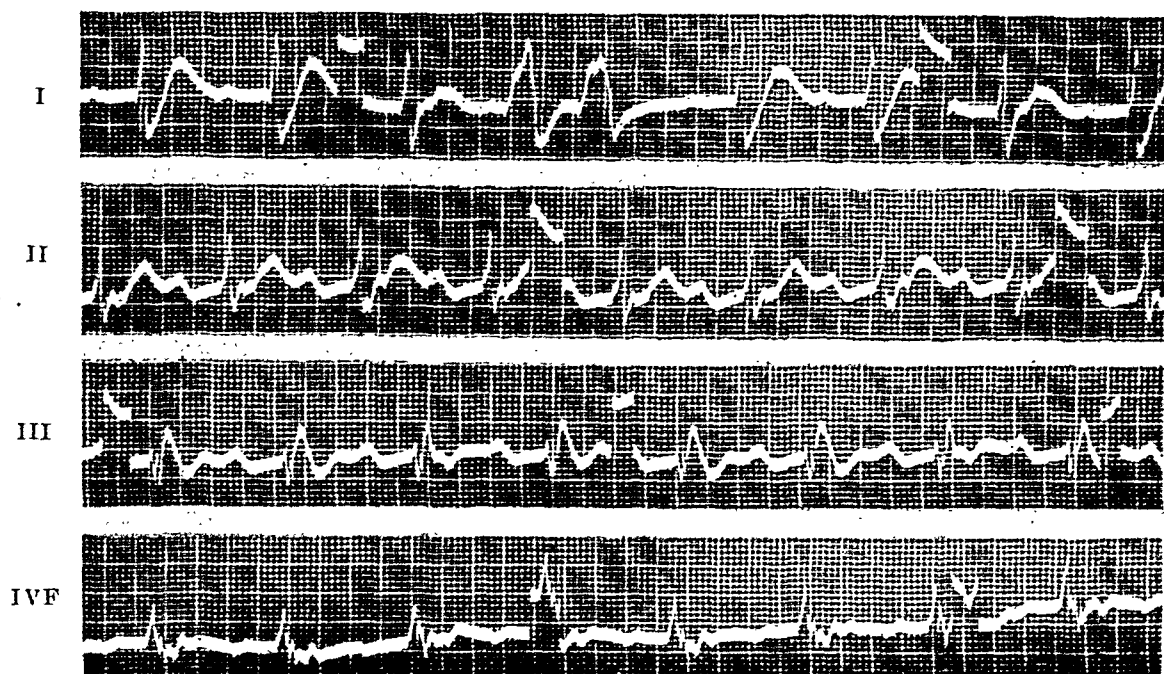


Fig. 4.—Period of 2:1 A-V heart block. The auricular rate is 142 per minute, the ventricular rate, 71 per minute. Two ectopic beats are present in Lead I. The P-R interval measures 0.38 second, the QRS complex, 0.12 second.

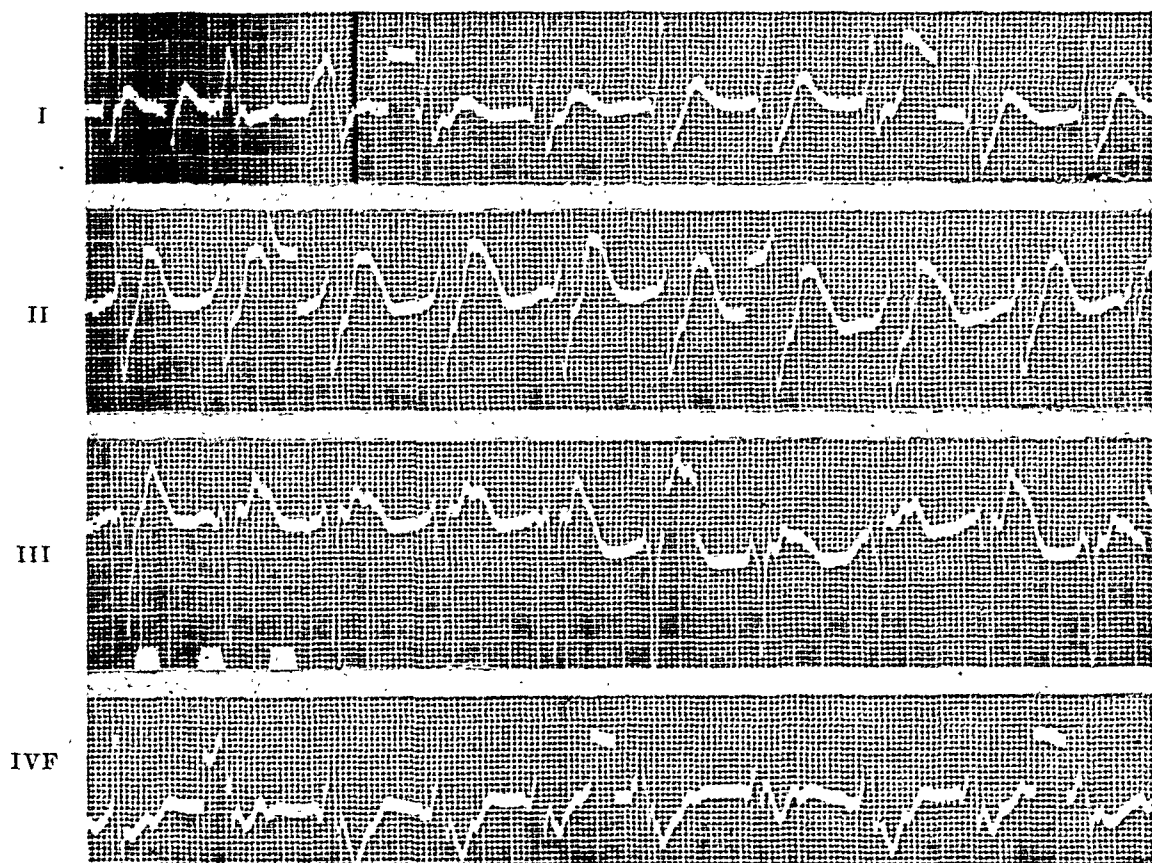


Fig. 5.—Final record. Total A-V dissociation. The auricular rate is 167 per minute, the ventricular rate, 75 per minute.

the first tracing (Fig. 1). It is important to note that the tachycardia was interrupted by a few beats of regular sinus rhythm in which both auriculoventricular and intraventricular conduction disturbances were present (Fig. 1, Lead III). This may be of significance in evaluating the later patterns of heart block and auriculoventricular dissociation because, although it is most likely that they were due to quinine, the possibility that these changes, too, may have resulted from the cocaine intoxication cannot be entirely discarded.

Except for a varying QRS pattern (Figs. 2,A and 2,B), the ventricular tachycardia persisted for one to one and one-half hours until the administration of the intravenous quinine. Although the quinine then periodically allowed a sinus mechanism to establish itself, this was accomplished only with considerable difficulty. In the early stages the ectopic ventricular pacemaker continually interrupted the attempt to maintain a sinus rhythm. Short runs of ventricular tachycardia between sinus beats, frequently resulting in trigeminal rhythm, occurred (Figs. 2,B and 2,C). Periodically, the tracing showed a complete return to the former continuous ventricular tachycardia (Figs. 2,F and 3,B). At times a partial auriculoventricular dissociation with auricular tachycardia and parasystolic rhythm appeared (Figs. 2,E and 3,D). A phase in which a bidirectional ventricular tachycardia existed was also noted (Fig. 3,A). At a later stage 2:1 A-V heart block was manifested for a prolonged period (Figs. 3,F and 4). Finally the total auriculoventricular dissociation became permanently established (Fig. 5) and remained unchanged thereafter.

The ventricular complexes were always abnormal, even when they occurred as a response to a supraventricular stimulus (Figs. 3,D and 3,E). This is undoubtedly the result of the cocaine reaction. As more quinine was administered the P-R interval became progressively prolonged, probably due to the retarding effect of quinine on auriculoventricular conduction. The varying degrees of auriculoventricular block most likely resulted from the same cause. It is possible, however, in view of the occurrence of an auriculoventricular conduction disturbance prior to quinine therapy, that these changes, too, may have resulted from the cocaine reaction or at least the cocaine may have potentiated the quinine effect.

It is interesting to note that previous descriptions of clinical cardiovascular effects of cocaine or novocaine simply mention "slowing of the heart rate,"^{5,6} "tachycardia,"^{5,6} or "sudden stoppage of the heart."⁷ As no previous electrocardiographic studies of such reactions have been made, accurate description of the types of arrhythmia is lacking. It is possible, in view of the electrocardiographic phenomena demonstrated in this patient, that similar arrhythmias have resulted from cocaine poisoning but have not been described in other than general terms because of lack of graphic representation.

The autopsy did not reveal any abnormal findings other than moderate passive congestion of the viscera. This has been reported as common to all cases of death following the use of local anesthetics.⁸ The absence of demonstrable underlying heart disease is further evidence of a primary idiosyncratic drug reaction.

Objection might be raised that the electrocardiographic changes are not comparable with those that have been obtained with the cocaine group of drugs in experimental animals. Mautz³ has demonstrated that local application of these drugs to the dog's heart results in a monophasic type of action current of short duration and a decrease in surface irritability of the heart. Burstein and Marangoni⁴ have also demonstrated reduction of myocardial irritability by the surface application of procaine. Watanabe¹ applied cocaine and novocaine to the sinus node of the frog's heart and obtained auriculoventricular dissociation. This was duplicated in the dog's heart by Shookhoff,² who also demonstrated right bundle branch block on injection of these drugs into the jugular vein of the dog and left bundle branch block when these solutions were introduced into a pulmonary vein. These methods, however, result in a direct toxic effect upon the myocardium and intrinsic conduction system and, as such, are not comparable to the effect demonstrated here which resulted from a primary central nervous system reaction with secondary reflex sympathetic cardiac stimulation.

SUMMARY AND CONCLUSIONS

A fatal case of acute idiosyncratic intoxication due to cocaine is described. Continuous electrocardiograms were obtained over a five-hour period. Ventricular tachycardia was the initial change recorded and, thereafter, auricular tachycardia, multifocal ectopic ventricular beats, bidirectional ventricular tachycardia, and auriculoventricular conduction disturbances occurred. All except the auriculoventricular conduction disturbances can be attributed to the cocaine reaction. It is probable that quinine therapy was responsible for the latter abnormalities, but the cocaine reaction cannot be entirely excluded as a responsible mechanism. The electrocardiographic changes due to cocaine are attributed to reflex central and peripheral sympathetic stimulation of the heart.

REFERENCES

1. Watanabe, T.: Untersuchungen über die Wirkung der ersten Stannius'schen Ligatur, *Ztschr. f. Biol.* 77:317, 1923.
2. Shookhoff, C.: Zur Kenntnis der Wirkung von Novocain, bez. Cocain auf das Säugetierherz, *Ztschr. f. d. ges. exper. Med.* 49:110, 1926.
3. Mautz, F. B.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, *J. Thoracic Surg.* 5:612, 1936.
4. Burstein, C. L., and Marangoni, B. A.: Protecting Action of Procaine Against Ventricular Fibrillation Induced by Epinephrine During Cyclopropane Anesthesia, *Proc. Soc. Exper. Biol. & Med.* 43:210, 1940.
5. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*. New York, 1941, The MacMillan Company.
6. Sollmann, T.: *A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology*, ed. 6, Philadelphia and London, 1942, W. B. Saunders Company.
7. Gilman, S.: The Treatment of Dangerous Reactions to Novocain, *New England J. Med.* 219:841, 1938.
8. Mayer, E.: The Toxic Effects Following the Use of Local Anesthetics, *J. A. M. A.* 82:876, 1924.

TUBERCULOMA OF THE MYOCARDIUM

A CASE REPORT

MAJOR S. M. RAUCHWERGER AND MAJOR R. J. ROGERS
MEDICAL CORPS, ARMY OF THE UNITED STATES

REVIEW of the literature indicates that cases of tuberculoma of the heart occur so infrequently as to warrant report of a single case. In the American literature, the latest report of true tuberculoma of the myocardium was that of Banyai and Van Hecke¹ in 1937. Cases of tuberculosis of the heart other than tuberculoma include Saffie's² report of a case of caseous tuberculosis in 1945 and Horn and Saphir's³ report of three cases of miliary tuberculosis of the myocardium in 1935, the latter having comprehensively reviewed the literature as of that date.

In the more recent foreign literature, Bose⁴ has reported a case of tuberculosis of the heart which he states, "to the naked eye, appeared as a neoplasm." In 1936, Masugi and co-workers⁵ reported the occurrence of granulomas resembling Aschoff bodies in the heart of a patient with pulmonary tuberculosis; and in 1937 Pfeil⁶ mentioned thirty-one cases of tuberculous involvement of the myocardium in 2,074 patients who died of tuberculosis. The following case is a rather classical one of tuberculoma of the myocardium, both from the clinical and pathologic point of view.

CASE REPORT

R. D., a 20-year-old colored World War II veteran, was admitted to this hospital on June 3, 1944, with the following history: Physical examination, including chest x-ray, showed essentially normal findings on induction into the service in March, 1943. About September, 1943, he began to complain of left pleuritic pain. Because of an elevated temperature he was admitted to the station hospital where examination revealed a left pleural effusion. Repeated aspirations of the left chest were negative for organisms until November, 1943, when tubercle bacilli were found. At this time the sputum was negative.

His chief complaints on admission to this hospital were pain in the left chest, weakness, loss of weight, and dyspnea. Physical examination revealed nothing remarkable. His weight was 144 pounds; height, 71 $\frac{3}{4}$ inches; blood pressure, 110/84; pulse rate, 96 per minute; and temperature, 98.6° Fahrenheit. There was restricted mobility of the left chest with diminished tactile fremitus, dullness to flatness on percussion, and absent breath sounds. Laboratory findings revealed tubercle bacilli in sputum and chest fluid.

In July, 1944, tuberculous involvement was discovered in the right lung and a right phrenicectomy was performed. At this time he began to experience abdominal distress manifested by gastric distention, diarrhea, and occasional bloody stools. Concomitantly, he developed cold abscesses of the back and of the anterior surface of the left chest. Smears from the abscesses were positive for acid-fast bacilli. At no time were there any complaints referable to the cardiovascular system and no electrocardiogram was made. Barium meal in February, 1945, was negative for any pathology. X-ray films of the spine and ribs were negative for caseous tuberculosis. Wasser-

From the Departments of Cardiology and Pathology, Veterans Administration, Oteen, N. C.
Received for publication July 18, 1946.

mann and Kline tests were negative. Blood count, urinalysis, and blood chemistry were all within normal limits. The erythrocyte sedimentation rate was 22 mm. in one hour. Repeated chest films revealed a small amount of fibrosis in the area of the first and second right intercostal space. The remainder of this lung showed no evidence of disease. The left lung was considerably compressed by fluid at the base. He gradually became cachectic and finally expired on Dec. 5, 1945. Clinical diagnoses were: Chronic moderately advanced pulmonary tuberculosis with serofibrinous involvement of the left pleura and multiple cold abscesses.

Autopsy Findings.—The body was that of a tall, undernourished colored man, 22 years of age. There was a sinus tract opening on the left posterior chest wall in the midscapular line about the level of the eighth rib. There was softening of the manubrium.



Fig. 1.—Circumscribed tuberculoma in the wall of the left auricle, showing close relationship to the base of the mitral valve.

The heart weighed 250 grams. There were three yellowish-gray nodules present; one located at the base of the mitral valve, 2 cm. in diameter (Fig. 1), and two others located in the myocardium of the left atrium which were somewhat smaller (Fig. 2). Heart valves were normal. The coronary vessels were patent and there was no thickening of their walls. The aorta was smooth.

There was a left empyema containing 400 c.c. of purulent fluid. Both lungs were adherent. The left lung was collapsed and weighed 500 grams. A few small tubercles were noted in the left apex. The pleura was thickened. The right lung weighed 300 grams. It was normal grayish pink on section, except for numerous shotlike tubercles scattered throughout the apex.

The spleen weighed 100 grams. Surface was normal and the cut section revealed a few small pinhead-sized tubercles. The parenchyma was smooth and dark red in color. The liver weighed 1,350 grams. The surface was smooth except for three or four fairly large tubercles averaging

0.5 cm. in diameter. Cut section revealed a mottled grayish-brown color. It was soft and friable. The gall bladder was normal.

The esophagus and stomach were grossly normal. There were numerous fairly large tuberculous ulcers present in the terminal ileum and in the cecum. The serosa of the entire bowel was studded with tubercles. The mesenteric nodes were large and caseous, most of them being the size of walnuts. The pancreas was normal.



Fig. 2.—Two small tuberculous nodules in the wall of the left auricle as seen after the splitting of the epicardium and sectioning.

Combined weight of the kidneys was 280 grams; a few fairly large light yellow tubercles were seen on the surfaces. Both adrenals showed almost complete replacement by large areas of caseation, so that almost none of the cortex remained intact. They were approximately four times normal size.

There was a large cold abscess surrounding the bodies of the entire thoracic spine which communicated with the sinus opening mentioned above. Within the abscess cavity, small particles of bone were noted floating free in the purulent material. The spine was sectioned longitudinally and the bodies of all the vertebrae showed caseous necrosis which was most extensive in the tenth, eleventh, and twelfth thoracic segments.

Histology: There were many typical tubercles and a few small areas of caseation in sections from the lungs. In sections from the heart, there were two large areas of caseation imbedded in the myocardium and completely surrounded by muscle cells. The caseated areas were within a zone of epithelioid cells in which a few giant cells of the Langhans' type were noted. In sections from the kidneys there were many hyaline casts in the tubules. There were areas of caseation necrosis and a few typical tubercles. In liver sections there were scattered tubercles; the sinuses

were filled with red cells and serum. There was massive replacement of the entire medulla and most of the cortex of the adrenals by areas of caseation. Many typical tubercles were seen in sections from the spleen.

DISCUSSION

Myocardial tuberculosis occurs in three main forms: (1) miliary, (2) nodular, and (3) infiltrating. Of these, the nodular variety as encountered in this case, is, relatively, the most frequent. This form usually occurs as yellowish-gray, rounded, fairly firm nodules which may vary in size from less than a centimeter to the size of an egg. They may be well defined or merged with the surrounding parenchyma. The common site is the wall of the right auricle. Their ability to produce symptoms, of course, depends upon their size and location. Most of the reported cases have been without subjective or objective signs of cardiac involvement, with a few notable exceptions. In Adamson's⁷ case, "the auricles were so markedly involved with multiple variously-sized masses, that it seemed they couldn't contract." The cases of Maurocordat^{8,a} and Townsend⁸ showed nodules of the auricles so large that the bloodflow in the pulmonary veins was obstructed, with resulting hemorrhage into the lungs and death from asphyxia. Binder⁹ reported a case in which there was obstruction to the auricular blood flow by a large tuberculoma of the left auricle. In Eisenmenger's¹⁰ case, a large tubercle about the size of a lemon in the wall of the right auricle caused compression of the auricular lumen. Banyai and Van Hecke's¹ report was similar to our case in that there was no clinical evidence referable to the heart.

SUMMARY

A case of nodular tuberculosis (tuberculoma) of the heart is presented, together with a summary of the recent literature. Although there were three nodules in the left auricle, one of which involved the base of the mitral valve, yet at no time was there any clinical evidence referable to the cardiovascular system.

REFERENCES

1. Banyai, A. L., and Van Hecke, L. J.: Tuberculoma of the Myocardium; Report of a Case, *Wisconsin M. J.* 36:721, 1937.
2. Saffie, S. F., and Valenzuela Garcia, R.: Tuberculosis del miocardio, *Rev. méd. de Chile*, 73:233, 1945.
3. Horn, H., and Saphir, O.: The Involvement of the Myocardium in Tuberculosis. Review of the Literature and Report of Three Cases, *Am. Rev. Tuberc.* 32:492, 1935.
4. Bose, A. C.: Tuberculosis of the Heart, *Indian M. Gaz.* 77:403, 1942.
5. Masugi, M., Murasawa, S., and Ya, S.: The Occurrence of Aschoff-body Like Granulomas in the Heart of a Patient With Pulmonary Tuberculosis, *Tr. Soc. path. jap.* 26:60, 1936.
6. Pfeil, K.: Contributions to Cardiac Pathology in Pulmonary Tuberculosis, *Beitr. z. Klin. d. Tuberk.* 89:161, 1937.
7. Adamson, W. W.: A Case of Tuberculosis of the Myocardium, *J. Path. & Bact.* 23:399, 1920.
8. Townsend, R.: Death From Asphyxia Caused by Large Tuberculous Masses Developed in the Parieties of the Left Auricle Compressing the Trunks of the Pulmonary Veins, *Dublin J. Med. Sc.* 1:176, 1832.
a. Maurocordat: Quoted by Townsend.⁸
9. Binder, H.: Tumorartige Tuberkulose des Hertzens, *Zentralbl. f. inn. Med.* 41:462, 1920.
10. Eisenmenger, V.: Zur Kenntnis der Tuberkulose des Herzmuskels, *Ztschr. f. Heilk.* 21: 74, 1900.

DAILY CHANGING PICTURE IN A CASE OF ACUTE RHEUMATIC CARDITIS

MAJOR HENRY J. WEINTRAUB AND LIEUTENANT COLONEL
LOUIS F. BISHOP, JR.

MEDICAL CORPS, ARMY OF THE UNITED STATES

IT IS well known that cases of acute rheumatic carditis show frequently changing pictures, but few examples have been found in the literature exhibiting marked daily electrocardiographic changes, probably because such serial tracings are not ordinarily taken. Pease, Steuer, and Peters¹ have called attention to the value of routine serial electrocardiograms in acute rheumatic fever; in bringing to light evidence of myocardial damage which otherwise might escape detection. They state that single electrocardiograms might prove confusing because of the presence of T waves very like "coronary T" waves. Myocardial involvement and pericarditis may remain unsuspected without serial electrocardiograms. They report three cases showing electrocardiographic evidence of cardiac damage which otherwise might have remained undetected. Pardee² has pointed out the large number (more than 60%) of cases of acute rheumatic carditis which show persistent T-wave changes suggestive of myocardial disease. Barnes³ has summarized the evidence on electrocardiographic changes in pericarditis, which points to the conclusion that the RS-T segment and T-wave changes in pericarditis, in most instances at least, are due to an inflammatory reaction in the subepicardial myocardium. Barnes also states that serial tracings, taken over a period of days or even weeks, may be necessary to distinguish the tracings of pericarditis from those of acute myocardial infarction.

A case of acute rheumatic carditis is reported in which daily electrocardiograms were taken over a twelve-day period, and after that time less often but still frequently, to demonstrate the daily reversible and recurring changes in RS-T segments, T waves, and QRS complexes. It is shown graphically by the electrocardiograms themselves how a single tracing could be confusing.

CASE REPORT

C. W., a 32-year-old white man, was admitted to the hospital where these studies were made on March 24, 1945. Family history and past history were essentially negative except for frequent colds and sore throats. Two weeks before admission he developed a cold and sore throat. Six days later he developed malaise, fever (101 to 102° F., oral), slight cough, chest pain, moderate sweating, and chilly sensations. He was given sulfatherapy at home for five or six days, without benefit, for "pneumonia." Upon admission he seemed toxic, and appeared acutely ill. Physical

examination revealed frank signs of a right lower lobe pneumonia (dullness to percussion, diminished breath sounds, increased voice sounds, increased tactile fremitus, and a few fine râles), with oral temperature of 102° F. No evidence of cardiac involvement was found. He received penicillin intramuscularly, 40,000 units every three hours for the first twenty-four hours after admission, without effect. He remained toxic, and x-ray films of the chest taken upon admission showed a clear right base with "thickened pleura" at the left base. On March 25, the day after admission, a to-and-fro moderately harsh friction rub was present over the cardiac apex and lower sternum. An electrocardiogram showed an elevation of the RS-T segment in Leads I and II, and a P-R interval of 0.26 second with a heart rate of over 100 per minute. That night, March 25, he developed pain, swelling, heat of both knees with voluntary muscular rigidity, and pain of the right elbow. Turbid fluid from the left knee gave a white blood cell count of 6,300 per cubic millimeter, with 88 per cent neutrophils. He was put on intensive salicylate therapy by mouth, with almost immediate marked improvement. On March 27, the temperature was 98° F., he was not toxic, felt well, the pulse rate was 84 per minute, and the lung fields were not abnormal to physical examination; he moved his elbow and knees freely, the knee joints showed no fluid clinically. From then until discharge, the patient felt well. However, he showed frequent changes in physical examination of the heart, in x-ray examination of the heart, and in serial electrocardiograms.

Frequent blood examinations between March 24 (the day of admission) and July 2 (nine days before discharge) revealed white blood cell counts ranging from 5,700 to 13,800 per cubic millimeter, with from 45 to 87 per cent neutrophils. Frequent sedimentation rates (corrected

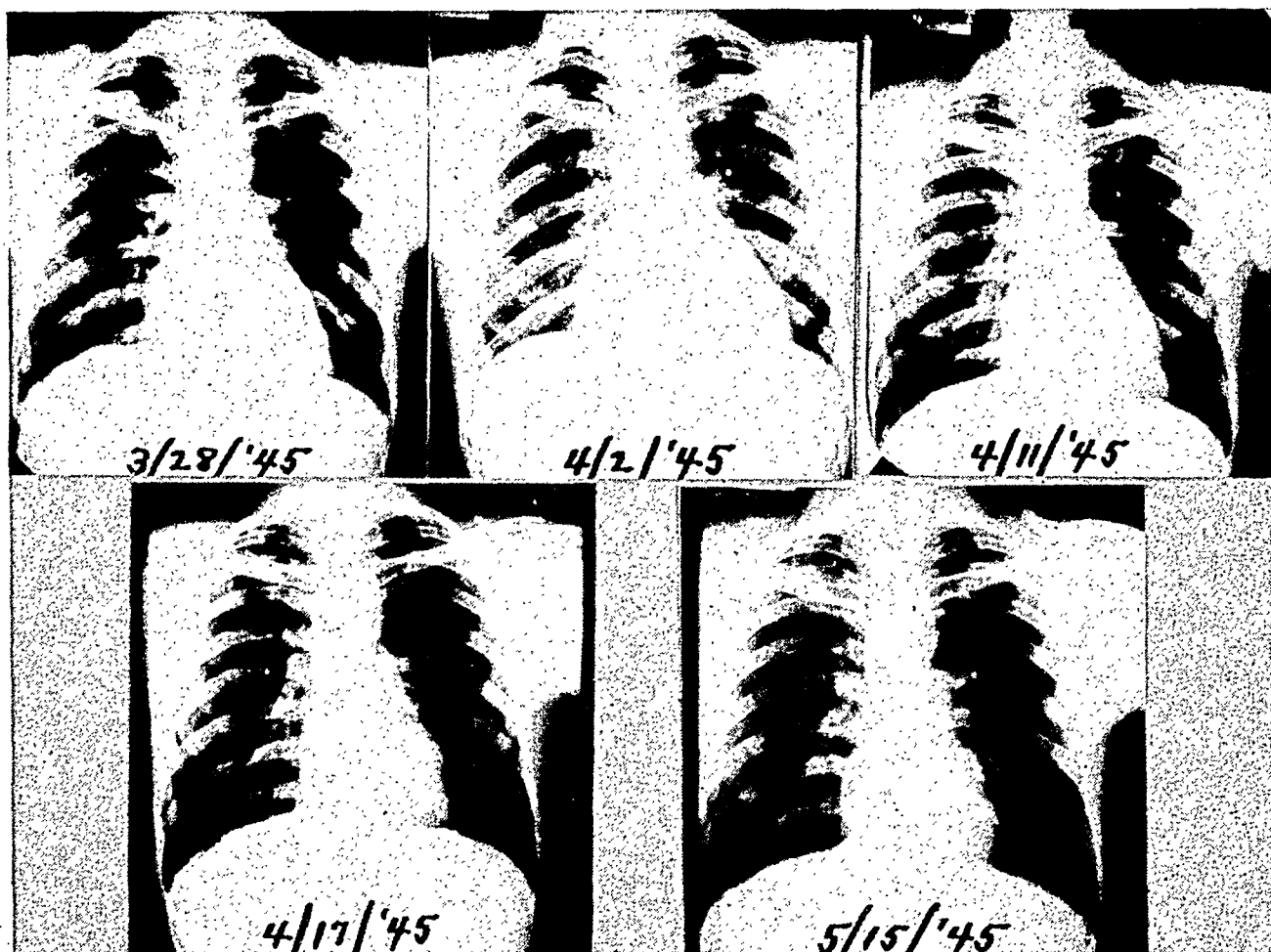


Fig. 1.—Teleroentgenograms (6-foot) x-rays taken during the course of the disease.

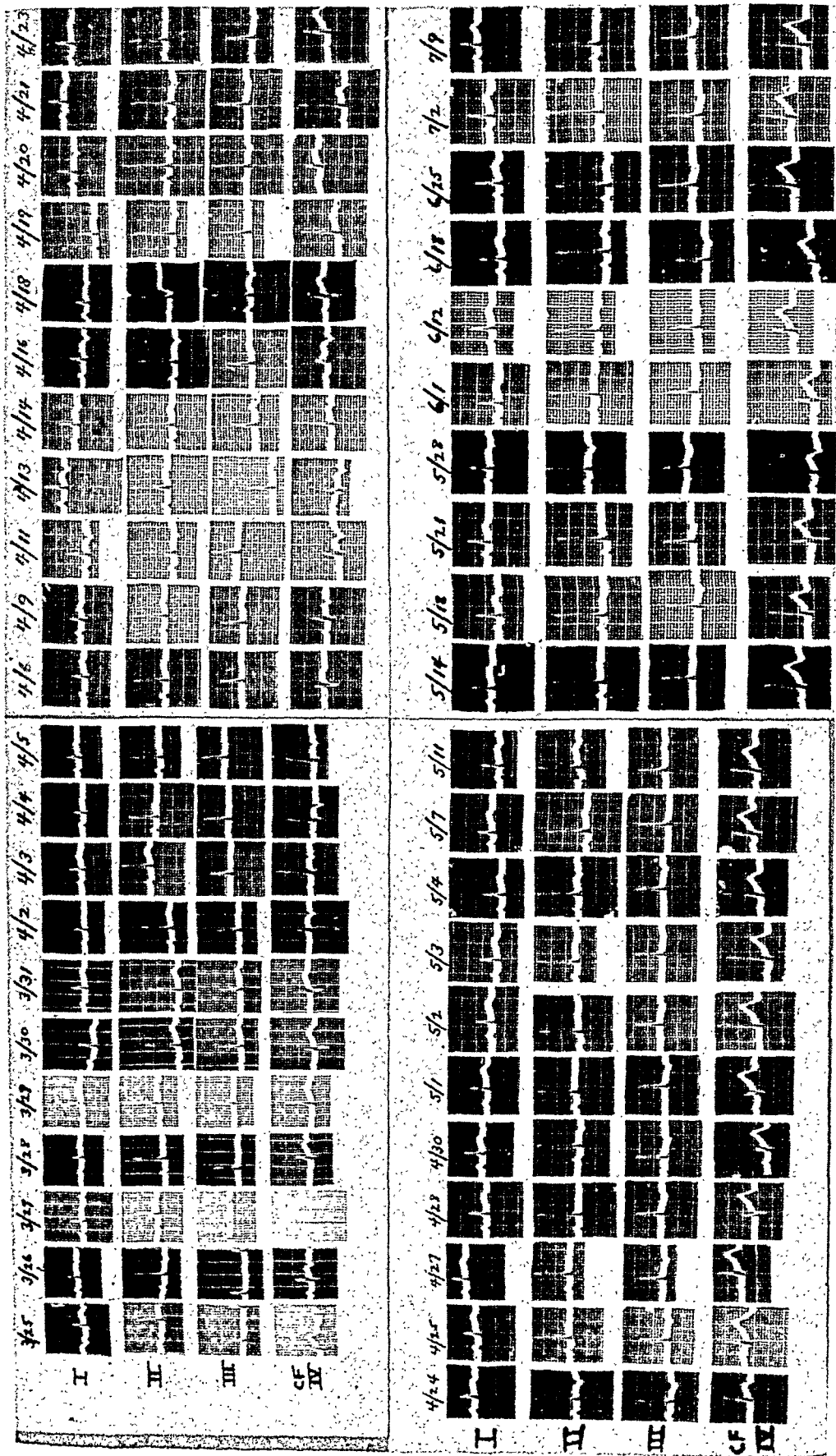


Fig. 2.—Serial electrocardiograms taken during the course of the disease.

for hematocrit) between March 26 and May 31 ranged from 18 to 43 mm. per hour (all but one determination being above 25 millimeters). From May 31 to July 2 there was a gradual decrease in the sedimentation rate to 4 mm. per hour.

COMMENT

Physical Examination of the Heart.—The pericardial friction rub changed frequently (often daily) in intensity and quality until it disappeared on April 10. On March 28, for the first time, a very soft apical systolic murmur was heard. The murmur changed often, and at times, daily in intensity, quality, and point of maximum intensity (apex and third left interspace next to the sternum) until May 14. From then until discharge a soft apical systolic murmur was heard.

X-ray Examination of the Heart.—Numerous teleroentgenograms were taken. During the course of the acute stage of the disease these showed an increase, and then a decrease to normal, of the cardiac shadow. These changes are illustrated in Fig. 1.

Electrocardiograms.—Serial electrocardiograms were taken, at first daily, then several times per week, and finally about once a week. At first, these tracings showed a constantly changing picture. Later, changes continued to appear, but less frequently. Involved in the changes were the P-R interval (generally prolonged), the T waves, the RS-T segments, the QRS complexes in Lead IV F, the heart rate, the amplitude of the QRS complexes in all leads, and the presence or absence of phasic sinus arrhythmia. The last few tracings showed stabilization with no change. They were essentially normal except for a low T wave in Lead II. The changing electrocardiographic picture is illustrated in Fig. 2.

Therapy.—Intensive salicylate therapy was continued from March 26 to April 23, and again from May 22 to May 31. Blood salicylate levels ranged from 6.9 to 62.8 mgm. per cent.

SUMMARY

A case of acute rheumatic carditis is reported to show the daily electrocardiographic changes during the acute phase of the disease. These changes occurred in the RS-T segments, T waves, and QRS complexes primarily, and were from day to day reversible and recurring. This changing picture indicates the interest and importance attached to the taking of serial tracings in cases of acute rheumatic carditis, for one tracing may be confusing diagnostically.

REFERENCES

1. Pease, Steuer, and Peters: The Value of the Electrocardiogram in Acute Rheumatic Fever, *Mil. Surgeon* 95:287, 1944.
2. Pardee, H. E.: *Clinical Aspects of Electrocardiograms*, New York, 1941, Paul B. Hoeber, Inc.
3. Barnes, A. R.: *Electrocardiographic Patterns*, Springfield, 1940, Charles C. Thomas.

ASYMPTOMATIC CONGENITAL ANOMALY OF THE HEART: CONGENITAL MUSCULAR CORD BRIDGING WALLS OF AURICLE ABOVE CENTER OF MITRAL VALVE

LIEUTENANT COLONEL W. L. McNAMARA AND LIEUTENANT COLONEL L. A. BAKER, MEDICAL CORPS, ARMY OF THE UNITED STATES, AND
KENNETH COSTICH, M.D., HINES, ILL.

WE CAN find in the literature no description of a case presenting anomaly of the heart similar to the variation which forms the basis of this report.

This anomaly, a muscular cord bridging the walls of the left auricle above the mitral valve, did not in any way disturb the function of the heart and was never the cause of clinical symptoms. It was discovered during routine examination of the heart at autopsy of a patient in whom death had been caused by cancer of the esophagus.

REPORT OF CASE

The patient was a Negro man, 54 years of age, who entered the hospital in the terminal stage of carcinoma of the esophagus. The Wassermann was negative. There was no history of syphilis or of heart disease.

Autopsy.—There was a carcinoma of the esophagus at the junction of the middle and upper thirds. It had caused obstruction and perforation with resulting suppurative mediastinitis. Metastases were demonstrated in the regional lymph nodes and mediastinum.

The combined weight of the kidneys was 400 grams. Both kidneys showed the same gross appearance. The capsules stripped with difficulty, but the surface was fairly smooth except for multiple cysts, the largest of which measured 8 mm.; the smallest was the size of a pinhead. These cysts were scattered throughout the cortex of the kidney and were noted in the parenchyma on section. The cysts contained clear fluid and were lined with a grayish glistening membrane. There was no evidence of arteriosclerosis or scarring. A diagnosis of multiple congenital cysts of the kidney was made. The bladder, prostate, vesicles, and testes showed no evidence of pathologic changes.

The aortic arch was smooth and there was practically no arteriosclerosis throughout the entire length of the aorta. The peripheral blood vessels were essentially normal.

The heart weighed 400 grams. There was a small amount of fibrous pericarditis. The muscle was somewhat softer than normal. There was no evidence of hypertrophy or dilatation. The coronary arteries were smooth. On section of the heart an anomaly was noted in the left auricle; a smooth round cord extended from one side of the wall immediately above the base of the mitral valve across the cavity to the other side in the same region. The cord was smoothly covered with endocardium continuous with that of the auricular walls. The two points of attachment to the walls were cone-shaped. The length of the cord arising from the apices and of the cones measured 3.5 centimeters.

The base of the cone-shaped attachment measured 3.5 mm. in diameter, and the diameter of the remainder of the length of the cord was 2 millimeters.

The valve leaflets were normal and showed no evidence of insufficiency to the water test.

There was no evidence of an inflammatory process either in the endocardium of the auricle or the endocardium covering the valve. The mitral valve measured 4 cm. across, parallel to the valve opening. The papillary muscles were normal. The aortic valve was normal in appearance, and the tricuspid and pulmonary valves presented no signs of abnormality. There was no endocardial thickening. No evidence of hypertrophy was noted.

Histologic examination of a section of the cord showed it to be composed of cardiac muscle, smoothly covered by endocardium. (Fig. 1.)



Fig. 1.—Opened left auricle showing muscular band bridging walls.

DISCUSSION

The structure of this cord would suggest conclusively that it was a congenital anomaly. No explanation is offered of its origin from the standpoint of embryology.

Stohr² in a study of malformations of the heart in the newborn concludes that the present view tends to assign the majority, if not all, of the congenital defects to abnormalities of development. However, she reports two cases of abnormal hearts in newborn infants in which, she felt, detailed histologic examinations tended to prove the inflammatory nature of the lesions.

In the case described in this paper, the structure was composed of an orderly arrangement of cardiac muscle covered by a smooth reflection of the endocardium of the auricle walls. There is nothing to suggest remotely an inflammatory process as an etiological factor.

Of special interest in this case is the occurrence of multiple congenital cysts of the kidney. In cases of congenital cardiac anomalies concomitant anomalies

in other organs of the body have frequently been noted. Thus, Vierordt (quoted by Stohr²) estimated that other anomalies such as harelip, syndactylism, horse-shoe kidney, and hypostadius are found in about 10 per cent of the cases of congenital heart disease.

Rannels and Propst¹ in a study of autopsy records at the Hospital of the University of Pennsylvania found thirty-six cases of cardiac congenital anomalies. In five of these cases there were associated congenital deformities.

SUMMARY

A congenital anomaly of the left auricle is described. There was a concomitant congenital defect of the kidneys. This cardiac anomaly produced no symptoms, and was accidentally discovered at autopsy on a patient who had died of carcinoma. A search of the literature has failed to show the report of a similar anomaly.

REFERENCES

1. Rannels, H. W., and Propst, J. H.: Incidence of Congenital Cardiac Anomalies Found at Autopsies Performed in Hospital of the University of Pennsylvania, *J. Tech. Methods* 17:113, 1937.
2. Stohr, Grete: Malformations of the Heart of the New-Born, *Arch. Path.* 17:311, 1934.

ERRATA

In the March, 1947, issue of the AMERICAN HEART JOURNAL, in the abstract entitled "The Effect of Age on the Clinical Effectiveness of Nitroglycerin Tablets," on page 401, the senior author's name was misspelled. It should be Sagall rather than Segall.

The following two errors appeared in the June, 1947, issue of the JOURNAL:

In the paper entitled "Significance of Abnormally Small QRS Deflections in One or More Precordial Leads" by Albert W. Lapin, M.D., on pages 754-756, in Table IV, under the columns headed Pleural or Pericardial Effusion or Ascites, Congestion or Edema of the Lungs, and Peripheral Edema, the dashes should be plus signs.

The ninth line of the third paragraph on page 760 should read "In this case Leads V_3 and V_6 ," etc. instead of "In this case Leads V_4 and V_6 ," etc.

Abstracts and Reviews

Selected Abstracts

Dack, S., and Moloshok, R.: Cardiac Manifestations of Toxic Action of Emetine Hydrochloride in Amebic Dysentery. Arch. Int. Med. 79:228 (Feb.), 1947.

The authors report nine patients, between the ages of 18 and 37 years, with amebic dysentery, who presented toxic effects following the administration of emetine hydrochloride. These patients were given between 7 and 22 grains of the drug. All but two patients developed some dyspnea or tachycardia, three developed apical systolic murmurs, and one developed gallop rhythm. Inversion of the T wave in two or more leads was recorded in all cases, and changes in the QRS complex were reported in two cases. The authors feel that patients who are taking emetine should be followed by electrocardiograms at short regular intervals.

The time of appearance of the electrocardiographic abnormalities also varied in each case, and was often delayed until one or two weeks following the discontinuation of treatment. Owing to this lag in the appearance of electrocardiographic changes, their absence cannot be safely utilized as a criterion for the continuation of emetine hydrochloride therapy beyond a certain dose.

Electrocardiographic abnormalities, when present, were of long duration, often persisting for two months or more following cessation of treatment. This suggested prolonged fixation of the drug in the myocardium or actual myocardial degeneration as the basis for the cardiac manifestations.

Toxic effects on the neuromuscular and gastrointestinal systems generally preceded the appearance of toxic cardiac effects. The former as well as the latter are indications for the discontinuance of further therapy with emetine hydrochloride.

HORWITZ.

Loewe, L., and Altire-Werber, E.: The Clinical Manifestations of Subacute Bacterial Endocarditis Caused by *Streptococcus s. b. e.* Am. J. Med. 1:353 (Oct.), 1946.

In a previous paper (J. A. M. A. 130:257, 1946) Loewe and co-workers described a new variety of a nonhemolytic streptococcus which was named *Streptococcus s.b.e.* In the present paper the authors report 115 consecutive and unselected patients with subacute bacterial endocarditis, of whom forty were infected with *Streptococcus s.b.e.* Of these forty patients, nine who were completely resistant to therapy died of the streptococcal infection, two died of congestive heart failure, and one developed a terminal *Staphylococcus aureus* infection. Four of these twelve fatalities were due to intracranial hemorrhage. Six of the remaining twenty-eight patients developed recurrence of infection, whereas there were no recurrences in the patients infected with other varieties of streptococci.

It was impossible to predict treatment success on the basis of in vitro penicillin sensitivity tests. Although the *Streptococcus s.b.e.* appeared to fall within the same range of in vitro sensitivity to penicillin as other streptococci, the total penicillin requirements and the treatment days for this organism far exceeded the quantity of penicillin and the treatment span required for infections due to *Streptococcus mitis* and *Streptococcus bovis*. Whereas these latter organisms were successfully treated by a dosage schedule of 500,000 units of penicillin daily for five weeks, the *Streptococcus s.b.e.* strain required two million units daily for eight weeks.

Whenever possible, the penicillin was given intravenously with heparin for prevention of venous thrombosis.

FRIEDLAND.

Kossmann, C. E.: Relative Importance of Certain Variables in the Clinical Determination of Blood Pressure. Am. J. Med. 1:464 (Nov.), 1946.

Four variables affect blood pressure in the arm as determined by the usual sphygmomanometric method. These are: the position of the subject (standing or recumbent), the venous content, the thickness, and the position of the arm. The position of the arm with reference to heart level is exceptionally important because of the hydrostatic pressure exerted by the column of blood between the heart level and the part of the vessel over which the Korotkoff sounds are ausculted. Thus, in 32 normal men the blood pressure in the brachial artery in the pendent arm exceeded by an average of 11.3 mm. Hg the pressure in the same arm when held at heart level.

The venous content of the arm affected blood pressure much less significantly. In the recumbent position the systolic pressure averaged 4.3 mm. Hg less "after drainage" than "before drainage" and the average diastolic pressure differences before and after drainage were negligible. In the standing position drainage did not significantly affect either systolic or diastolic pressure in the arm held at heart level. In the pendent arm the systolic pressure did not change "after drainage" but the diastolic pressure was lower by an average of 3.3 mm. of mercury.

A significant correlation was found to obtain between the circumference of the arm and the diastolic pressure. There was no correlation between this factor and the systolic pressure. The fact that the blood pressure in the two arms is different is mentioned but no data are given.

FRIEDLAND.

Webb, A. C.: Truncus Arteriosus Communis Persistens. Arch. Path. 42:427 (Oct.), 1946.

The author reports the thirty-eighth recorded case of truncus arteriosus communis persistens. This anomaly was found in a 6-month-old white male infant who, from the time of birth, had cyanosis and dyspnea. Death was caused by acute respiratory infection terminating in bronchopneumonia.

Necropsy showed a centrally placed heart, from the base of which a single great vessel made its exit. The ostium of this common aorta (truncus) was immediately above a ventricular septal defect and approximately two-thirds over the right ventricle. There was also a patulous foramen ovale and a deformed tricuspid leaflet. The blood supply to the lungs was provided by two arterial branches of a patent ductus arteriosus. No fibrous cord indicative of pulmonary artery atresia could be found. The highly characteristic four semilunar leaflets were not present in this case, and the author emphasizes (as did Abbott) that this finding is not essential to diagnosis.

GOULEY.

Pratt-Thomas, H. R.: Tuberos Sclerosis With Congenital Tumors of Heart and Kidney. Report of a Case in a Premature Infant. Am. J. Path. 23:189 (March) 1947.

The author presents the case of a premature Negro infant (eighth month) who died three days after delivery. It breathed spontaneously after being normally delivered, and was apparently well until the third day when cyanosis became marked and respiration difficult. The mother, 19 years old, had shown in this, her first pregnancy, leg edema, marked albuminuria, and hypertension. Serologic tests for syphilis were negative.

The child weighed 1,655 grams, was small and poorly developed. Necropsy revealed striking lesions of tuberous sclerosis in the heart and brain. A smooth round tumor projected from the apex of the heart. Very small nodules were noted in the right auricle and ventricle; all of them were pale reddish-tan, generally well demarcated. Multiple nodules were scattered throughout the brain, the most prominent being in the right frontal lobe.

Microscopic examination showed the cardiac nodules to be composed of huge cells, round or oval, the cytoplasm of which was completely clear or else finely granular. Mitosis was not seen. Striated myofibrils often radiated from central nuclei, so-called "spider cells." Cross striations were evident. Many very small nodules blending with normal myocardium were seen microscopically. Best's carmine stain revealed glycogen in the cytoplasm of some of these

cells, even in tissue preserved in formalin for eighteen months. The brain nodules showed changes including gliosis and degeneration involving both nerve and glial cells. One nodule was truly neoplastic.

Kidney section revealed focal tubular dilatations, a feature noted in many of these cases.

The author comments (as did other writers) on the close relationship between cardiac rhabdomyoma and tuberous sclerosis. Of interest is the rarity of this process in the Negro race.

GOULEY.

Saphir, Otto: Myocardial Granulomas in Subacute Bacterial Endocarditis. Arch. Path. 42:574 (Dec.), 1946.

In a discussion of myocardial granulomas in subacute bacterial endocarditis, Saphir emphasizes the nonspecific aspects of the Bracht-Wächter lesions. He has found Aschoff bodies in 34 per cent of a group of fifty-five cases of subacute bacterial endocarditis, mostly in adolescents. In fatal cases treated with sulfa drugs and with penicillin, he has noted small foreign body granulomas surrounding a central deposit of calcium. These were scattered throughout the myocardium; they did not contain bacteria.

Saphir believes that these calcific foreign body granulomas are of embolic origin, arising from healing vegetation on the valves undergoing calcification. He saw small calcific particles in arterioles which he considered to be further evidence of their embolic origin.

A critical consideration of the literature on Bracht-Wächter bodies indicates that they signify no definite entity and that, therefore, the term "Bracht-Wächter body" should be discarded.

GOULEY.

Resano, J. H.: Dysphagia Caused by Aortic Aneurysm Treated by Ligation of the Descending Thoracic Aorta and Forward Displacement of the Esophagus by Forming a New Hiatus. Rev. clín. españ. 21:479 (June), 1946.

A case is described in which there was present extreme dilation of the ascending and descending portion of the aorta which produced displacement and stenosis of the esophagus resulting in dysphagia. Compression of the esophagus occurred at an area of relative aortic stenosis between the dilated ascending and descending portions of the aorta. At operation a cellophane band was placed around the aorta at the site of esophageal pressure and the esophagus was separated from the aorta and moved anteriorly by forming a new hiatus in the diaphragm. Following operation dysphagia disappeared. An angiocardigram taken one year after the operation revealed a coarctation of the aorta at the site of the ligature.

HECHT.

Alvarez Mena, S.: The Normal Esophageal Electrocardiogram. Rev. cubana de cardiología 7:73 (April-June), 1946.

Unipolar esophageal leads were obtained from twenty-five normal individuals. Large biphasic auricular deflections were recorded when the exploring electrode was located 30 to 35 cm. from the teeth. These records exhibited an intrinsic auricular deflection demonstrating the arrival of the action current underneath the exploring electrode. The ventricular deflections revealed small Q waves (less than 3 mm.) at ventricular levels, given as 55 cm. from the teeth. When the electrode was moved cephalad, the Q waves increased in amplitude and at auricular levels a deep QS deflection was noted in 40 percent of the cases. Maximum height of R was noted at levels 50 cm. from the teeth, S waves were inconstant, and T waves were always positive. The small Q waves observed at ventricular levels are interpreted as evidence of early activation of the right side of the interventricular septum.

HECHT.

Alzamora Castro, V.: Observations on the Significance of Changes of the ST Segment and the T Wave. Gac. méd., de Lima 9:285-309, 1946.

In patients with evidence of coronary artery disease a standard exercise test may change the direction and shape of the T waves. A flat T wave may become upright and a biphasic or inverted T wave may change toward a more "normal" pattern. It is assumed that a "fatigue factor A,"

present in or released by the heart muscle during stress, is capable of altering the balance of electrical forces during the process of reactivation. Under these conditions an upright T wave may reflect a more abnormal myocardial state than an inverted T wave. Examples of records taken during episodes of acute anginal pain reveal a reversal of a previously inverted T without significant elevation of the S-T segment in many unipolar precordial leads. Reversal of a previously inverted T in V_R was frequently noted. HECHT.

Jimenez-Diaz, C., Arjona, E., Ales, J. M., Grande, F., Lopez Garcia, E., and Oya, J. C.: The Influence of Alterations of Bloodflow Through the Lesser Circulation Upon Volume and Elasticity of the Lungs. Rev. clín. españ. 21:207 (May), 1946.

Perfusion experiments on isolated lungs of dogs demonstrated that overloading of the vascular system of the lungs resulted in increased aeration of the lungs similar to that seen in acute pulmonary emphysema. Under these experimental conditions the lungs appear to be more rigid and resemble the state observed in experimental asthmatic shock. It is concluded that both bronchial and "cardiac" asthma may result from acute overloading of the lesser circulation. HECHT.

Ortiz de Landazuri, E., Perianes Carro, J., and Merchante Iglesias, A.: Treatment of Subacute Bacterial Endocarditis With Penicillin. Rev. clín. españ. 22:466 (Sept.), 1946.

Fourteen patients with subacute bacterial endocarditis in the bacteremic phase were treated with sodium penicillin. Nine recovered from the acute phase of the disease and the cases may be considered to be arrested. The dosage ranged from 100,000 to 750,000 units daily with a total from 1 to 52 million units. The duration of treatment was short; the longest period covered 135 days (death), the shortest seven days (survival). Penicillin was administered without anticoagulants by intermittent intramuscular or intravenous injections and by continuous intramuscular and intravenous drip infusions. Sodium benzoate was added (10 Gm. per day) when a clinical response was not readily obtained from penicillin alone. There was no apparent correlation between the response to treatment and the number of colonies per c.c., the severity of the clinical symptoms, and the dose of penicillin. HECHT.

Mugica Echarte, J.: The Functional State of the Vascular System in Pulmonary Tuberculosis. V. The Lungs as Blood Depots. Rev. clín. españ. 21:403 (June), 1946.

In nine patients suffering from pulmonary tuberculosis in whom a pneumothorax was induced and in one additional patient, in whom an artificial paralysis of the phrenic nerve was induced, the blood volume increased considerably after the procedure. The total circulating blood volume rose from an average of 4,600 to 6,350 ml., circulating plasma volume from 2,530 ml. to 3,400 ml., and blood volume per kilogram of body weight from 77 ml. to 104 milliliters. The volume of packed red cells did not change appreciably. It is assumed that the lungs function as blood depots and discharge their contents when collapse therapy is instituted. HECHT.

Duffau, G., and Sepulveda, M.: Rheumatic Nodules in Children. Arch. d. Hosp. niños Roberto del Río 14:127 (Sept.), 1946.

Twenty-eight of 186 children admitted to the hospital during a six-year period with the diagnosis of acute rheumatic fever exhibited typical rheumatic nodules. They were most frequently localized at elbows and knees. All but one of the children with nodules had evidence of rheumatic heart disease. There was no correlation between the number and size of the nodules and the type or severity of the cardiac lesion, but it appeared that nodules were more frequent in children suffering from recurrent attacks of rheumatic fever. Nine of the twenty-eight patients died while under observation (33 per cent as compared to 16 per cent for the entire series). HECHT.

Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man With Tetraethylammonium. Preliminary Observations on its Clinical Application. *Am. J. M. Sc.* 213:315 (March), 1947.

Tetraethylammonium, a quaternary ammonium ion, was found by Acheson and Moe to block transmission of nerve impulses through autonomic ganglia in animals. This report concerns itself with the effects of such autonomic blockade in man and presents preliminary observations concerning its usefulness as a diagnostic and therapeutic agent in various disease states.

The drug was administered in doses of 0.2 to 0.5 Gm. intravenously, or up to 20 mg. per kilogram of body weight intramuscularly. The effects on the cardiovascular system were primarily the result of the release of vasoconstrictor tone; there was an increase in skin temperature, a transient fall in both systolic and diastolic pressure, postural hypotension, a fall in peripheral venous pressure, and an increase in heart rate and output. In two cases of acute myocardial infarction intravenous administration dramatically relieved the pain without the development of further changes in the electrocardiogram, despite a significant fall in blood pressure. The circulatory effects have been applied clinically in peripheral vasoconstrictor states, in relief of pain due to ischemia, in the relief of vasospasm, and as a diagnostic procedure. The effects in the gastrointestinal tract consisted of a cessation of normal peristalsis and a diminution in gastric secretion. This was applied clinically in the relief of pain and increased motility. Other effects included decrease in salivary secretion, cessation of sweating, incomplete dilatation of the pupil with loss of accommodation, decreased bladder tone, and abolishment of the urge to void. There was a significant relief of pain in causalgic states, which in a few instances failed to return after the immediate effects of the drug had disappeared. Toxic effects have been chiefly due to the ganglionic blocking action of the drug.

It is concluded that tetraethylammonium is a useful tool for the further study of disorders affecting the autonomic system, and that it is helpful in the selection of patients in whom surgery on the autonomic nervous system is to be considered. In selected cases the use of the drug may be of therapeutic as well as diagnostic value, especially in peripheral, vascular, and causalgic states. Though it will produce a transient fall in arterial pressure and has relieved symptoms of the complications of hypertension in a few instances, treatment of hypertension by repeated use of the drug does not appear feasible.

DURANT.

Mayock, R. L., and Rose, E.: Insensitivity to Epinephrine in a Patient With a Functioning Tumor of the Adrenal Medulla. *Am. J. M. Sc.* 213:324 (March), 1947.

A 42-year-old man had had attacks typical of paroxysmal hypertension for two and one-half years. At surgery a right-sided pheochromocytoma was removed which was found to contain 76.5 mg. of free epinephrine. Prior to surgery, doses of epinephrine up to 1.5 c.c. subcutaneously produced no rise in blood pressure. Following removal of the tumor there was a return of normal sensitivity to epinephrine. It is suggested that the demonstration of epinephrine insensitivity may serve as a useful and harmless test for the diagnosis of functioning tumors of the adrenal medulla.

DURANT.

Cameron, D. E.: Increased Reactivity Caused by Adrenalin. *Am. J. M. Sc.* 213:331 (March), 1947.

Administration of excessive amounts of adrenalin may result in severe head- and neckaches, in transitory blanching of the injected vein together with the appearance of goose pimples, and in the persistence for several days of an increased pressor response to adrenalin. It seems reasonable to compare these findings with the situation which exists where the individual is exposed to repeated psychic traumata with repeated participation of the adrenosympathetic system, such as occurs in combat experience or in prolonged involvement in a guilt or other conflict situation. In these situations, as in those presented in the report, there frequently results an increased reactivity of those structures which react to the adrenosympathetic system. But these two situations differ in that the psychic traumata are repeated over long periods and lead, in a pro-

portion of cases, to such a degree of increased reactivity that response occurs to ordinary everyday stresses, resulting in the establishment of a self-perpetuating autonomous anxiety state.

DURANT.

Ruskin, A., and Decherd, G. M.: Thiamine Circulation Time. *Am. J. M. Sc.* 213:337 (March), 1947.

Thiamine hydrochloride, in a standard supraoptimal dose of 300 mg., is a safe and exact subjective method for determining the speed of blood flow from arm to tongue. The normal circulation time by this method is 4 to 8 seconds in children and 5 to 13 seconds in adults. Studies have been made in 295 different cases, and values recorded for various grades of congestive heart failure and other disorders.

Circulation time, determined by any clinically used method, varies inversely with the dosage of the drug until a point is reached which may be called the true or shortest circulation time. This point is usually reached at a dose level of 200 to 300 mg. of thiamine, and may not be reached at the maximum safe dosage of 1 Gm. of magnesium sulfate, 0.48 Gm. of aminophylline, or 5 c.c. of 20 per cent decholin. Another source of error in doing circulation times with volumes of solution 5 c.c. or greater is the shortening apparently resulting from the rapid injection of these amounts under pressure. The thiamine method has the disadvantage of requiring the cooperation of the subject and the injection of rather large doses of the drug. It has the advantage of simplicity, safety, and exactness. In case of failure to respond to the 300 mg. dose, 600 mg., 900 mg., and even larger doses may be safely injected. To prevent another failure or delay in response, an interval of at least two hours between injections has been found satisfactory. Although no serious allergic or anaphylactic reactions have been encountered in more than a thousand injections, reports in the literature have emphasized the importance of a preliminary skin test, as well as the avoidance of an interval of one or two weeks between injections, as prophylactic measures.

DURANT.

Steiner, A., and Kendall, F. E.: Atherosclerosis and Arteriosclerosis in Dogs Following Ingestion of Cholesterol and Thiouracil. *Arch. Path.* 42:433 (Oct.), 1946.

The authors discuss the inability to produce experimental cholesterol atherosclerosis in dogs comparable to that seen in rabbits. They state that hypercholesterolemia produced in dogs by high cholesterol (egg yolk) diets and by high fat diets will not give rise to atherosclerotic lesions. They, therefore, investigated cholesterol metabolism by altering thyroid function, knowing that marked hypercholesterolemia follows cholesterol feeding to thyroidectomized dogs. Surgical approach to the problem was difficult because of secondary malnutrition.

The authors, working with a group of four dogs, after control periods of two months of thiouracil alone, gave high cholesterol (in cottonseed oil) plus thiouracil up to 1.2 Gm. daily for fourteen months. The administration of thiouracil resulted in blood cholesterol elevations comparable to those obtained after thyroidectomy. The addition of high cholesterol diet in three of these dogs resulted in very high blood levels, and in one dog a higher level than any previously recorded.

Autopsy revealed typical atherosclerotic lesions in the aorta, the coronary, the thyroid arteries, and, to a lesser degree, in many other arteries. This was notable in the three dogs receiving the combined diet and thiouracil treatment. The fourth dog, which received thiouracil alone throughout the entire fourteen month period, showed thyroid enlargement similar to that in the other dogs, but did not have atherosclerosis. The authors point out the similarity of this type of atherosclerosis to that of human atherosclerosis in its location and morphologic character.

GOULEY.

West, H. F.: Heart Disease in the Case-Finding Program. *Am. Rev. Tuberc.* 54:465 (Dec.), 1946.

Hundreds of x-ray films of the chest are being recorded daily throughout the nation and are accepted as the most accurate and rapid procedure for detecting early tuberculosis. Such roentgenograms obtained in mass surveys are being studied by various groups in order to deter-

mine their value in disclosing evidence of heart disease. These studies are of value in disclosing unsuspected cardiac enlargement due to hypertension or valvular lesion, pericardial disease, congenital anomalies, aortic arteriosclerosis, and other abnormalities.

For the past three years the Heart Division of the Los Angeles Tuberculosis and Health Association has participated in the case-finding project of the Industrial Health Program. From May, 1943, through February, 1946, a total of 63,398 persons have been x-rayed. In this series the interpretation of suspected tuberculosis was 2.7 per cent and of suspicious heart abnormalities, 2.0 per cent.

This author suggests that a joint committee, composed of members of the National Tuberculosis Association and the American Heart Association, be created to consider the value of this procedure, and if approved, to establish minimum standards or criteria for such surveys.

BELLET.

Burke, P. J.: Penicillin Prophylaxis in Acute Rheumatism. *Lancet* 7:25 (Feb. 15), 1947.

The author treated ten rheumatic patients prophylactically with penicillin by mouth for a year and compared the clinical findings with those in an untreated group of similar patients. Rheumatic manifestations were five times more frequent, and throat infections six times more frequent, in the untreated group than in the treated group.

BELLET.

Braun, K., Roth, I., And Suesskind, S.: Intraventricular Block in Malnutrition and Vitamin B Deficiency. *J. Pediat.* 30:177 (Feb.), 1947.

The most commonly described electrocardiographic changes in vitamin B deficiency are depression and inversion of the T waves, prolongation of electrical systole, low voltage of the ventricular complexes, and premature beats. These changes have also been described in pellagra. The authors encountered two cases of malnutrition and vitamin B deficiency which showed intraventricular block. Both patients, a fifteen-month-old boy, and a five-year-old girl, showed widened QRS complexes. Both also showed T-wave changes. They were treated with liver extract, blood transfusions, vitamin B₁, and niacin. After nine and five days of treatment, respectively, both patients had normal electrocardiograms.

Reversible intraventricular block is rare and is encountered in acute heart failure, acute coronary insufficiency, acute infections, diphtheria, and digitalis overdosage. The question arises as to whether or not the changes in the myocardium are of metabolic origin, or whether they are organic in nature. The authors feel that the rapid electrocardiographic improvement observed in these patients suggests that the abnormalities were due to metabolic disturbances affecting the intraventricular conduction system.

HAUB.

Erganian, J. A., Forbes, G., and Case, D.: Salicylate Intoxication in the Infant and Young Child. *J. Pediat.* 30:129 (Feb.), 1947.

Thirteen cases of salicylate intoxication were studied in infants and children ranging from 3 weeks to 3½ years of age. Laboratory determinations included plasma and spinal fluid salicylate concentration, pH of the blood serum, carbon dioxide content of the serum, prothrombin time, urine examination, and other procedures. The amount of salicylate ingested was determined in most instances by inquiry; this amount varied from 15 grains in two days to 126 grains in three days. Almost all the patients had received salicylates for either a cold or a cough. Clinically, they exhibited temperatures of from 38 to 40° C., were either pale or cyanotic, somewhat dehydrated, apathetic or stuporous, and showed some type of abnormal respiration. Other manifestations were: expiratory stridor, tarry stools, xanthochromia, twitchings, and convulsions. Plasma salicylate concentrations varied from 1.7 to 68.5 mg. per cent. In most of the cases, the amount of salicylate administered was greater than the limits of safety recommended by Marriott and Jeans (one grain per year of age every four hours). The carbon dioxide content of the serum was uniformly depressed and varied from 14 to 38 volumes per cent on admission. All patients received M/6 sodium *r*-lactate in Ringer's solution by the intravenous and subcutaneous route immediately on admission to the hospital and, in addition, were given parenteral vitamin K and vitamin C. Small whole blood transfusions were given to combat hemorrhagic tendencies. The patients

in severe acidosis were also in a state of circulatory collapse and were, therefore, also given oxygen. One patient died; permission for necropsy was not obtained.

The authors also studied the absorption curves of both acetyl salicylic acid and sodium salicylate in a group of children. The single dose absorption curves indicated that there probably would be a tendency toward accumulation of salicylate in the blood when administration was continued over a period of days. This assumption was borne out by further experiments.

In the absence of renal failure, diarrhea, diabetes, and other severe infections, the combination of hyperpnea, listlessness, and fever should suggest salicylate intoxication as a likely diagnosis. Because of the serious and progressive nature of such intoxication, emphasis is placed upon early diagnosis, frequent biochemical determinations, and prompt treatment. HAUB.

Poliakoff, H.: Mild Rheumatic Reaction in Coast Guard Recruits. Am. J. M. Sc. 213: 37 (Jan.), 1947.

Each winter and spring a high incidence of acute ankle arthritis has been noted at the Coast Guard Training Station at Manhattan Beach. An analysis of the 1945 outbreak led to the conclusion that this is a mild manifestation of rheumatic fever. Of the fifty-two cases of rheumatic fever in the 1945 epidemic, 54 per cent ran a significantly similar course characterized by transient mild ankle arthritis with a paucity of other symptoms. Careful analysis of these mild cases showed definite rheumatic stigmata in thirteen (25 per cent). Of the twenty-nine cases in which electrocardiograms were taken, transient carditis was in evidence in five. The localization of the rheumatic fever manifestations to the ankles was attributed to local static and traumatic factors incident to recruit training. DURANT.

Chambers, W. N.: Blood Pressure Studies in 100 Cases of Coronary Occlusion With Myocardial Infarction. Am. J. M. Sc. 213:40 (Jan.), 1947.

In an analysis of 100 cases of myocardial infarction it was found that the incidence of antecedent hypertension was greater (74 per cent) than in the general population. There was no relation between antecedent hypertension and the mortality rate in coronary occlusion, but in the hypertensive group the mortality was directly proportional to the degree of hypertension. Hypertension at the onset of the attack was a common finding (53 per cent) and occurred more frequently (68 per cent) in the fatal group. Hypotension in the initial reading was found in only 18 per cent. A fall in blood pressure occurred initially in 63 per cent, but all cases showed a fall at some time during the illness, although the fall often remained within hypertensive limits. An early return of the blood pressure to normal or preocclusion hypertensive levels was found to be a good prognostic sign. In the fatal group it usually did not return to its former level. The number of survivors who regained their original hypertension increased as the time elapsed after the occlusion, 58 per cent having regained their hypertension by the second year. After recovery from the initial coronary occlusion, the height of the blood pressure had no relationship to the frequency of recurrence or the ultimate prognosis. DURANT.

Gubner, R., DiPalma, J. R., and Moore, E.: Specific Dynamic Action as a Means of Augmenting Peripheral Blood Flow; Use of Aminoacetic Acid. Am. J. M. Sc. 213:46 (Jan.), 1947.

The effect on the peripheral blood flow of the ingestion of 20 Gm. of glycine dissolved in 200 to 300 c.c. of water or milk was investigated in twenty-five subjects, including nine patients with peripheral vascular disease. A rise in surface temperature was observed in the three regions tested; toes, fingers, and forehead. A significant increase in the temperature of the toes occurred in eleven normal subjects tested, and in three of four cases with peripheral vascular disease. The temperature of the fingers similarly increased in fourteen of fifteen cases. Forehead temperature increased in six of nine cases tested.

The temperatures attained, fully equivalent to the effect of posterior tibial nerve block in six cases in which comparison was made, indicate maximal vasodilatation. The effect exceeded that of alcohol in four cases in which the comparison was made between the ingestion of glycine and 2 ounces of whiskey. Oscillometric pulsation in the calf increased in eight of eleven normal sub-

jects, but no appreciable increase was observed in three cases with peripheral vascular disease. Blood flow to the extremities, as determined by venous occlusion plethysmography, was increased in eight of ten subjects examined, including four of five cases with peripheral vascular disease. The average increase was 62 per cent in the normal subjects and 30.5 per cent in those with peripheral vascular disease.

The increase in blood flow is an accompaniment of increased heat production (mainly in the liver) with attendant peripheral vasodilatation and increased cardiac output resulting from the specific dynamic action of glycine. The average maximal increase in oxygen consumption above the basal level in eighteen cases studied was 18.4 per cent; the greatest individual rise was 52 per cent. The effect of glycine on oxygen consumption and on peripheral blood flow is manifest in one hour and is maximal after two to three hours. * The specific dynamic action of glycine persists for a period of five to seven hours.

It is concluded that the ingestion of glycine provides a simple physiologic means of accomplishing an effective and sustained increase in peripheral blood flow. DURANT.

Friedman, N. B., Lange, K., and Weiner, D.: The Pathology of Experimental Frostbite. Am. J. M. Sc. 213:61 (Jan.), 1947.

This study represents an attempt to correlate the morphologic aspects of the reactions of tissues to cold with modern physiologic concepts of the effects of low temperatures. It was found that the fundamental lesions of experimentally produced frostbite in rabbits are vascular. The formation of agglutinative erythrocytic thrombi lead to vascular occlusion and ischemic gangrene. While heparin did not prevent the early clumping of red cells within the vessels, it apparently did prevent the development of true agglutinative thrombi from the clumped erythrocytes by interfering in some way with the adhesiveness of the packed red cells; consequently, vascular lesions did not appear, and gangrene did not ensue. No changes in nerve or muscle attributable directly to cold were observed. DURANT.

Porter, W. B.: The Effect of Patent Ductus Arteriosus on Body Growth. Am. J. M. Sc. 213:178 (Feb.), 1947.

This study concerns three patients with patent ductus arteriosus, aged 23, 34, and 11 years, respectively. Charts are presented comparing height, weight, and surface area with the other members of the family in the first two cases, and with a normal identical twin in the third. The charts show these patients to have been definitely influenced by some factor resulting in positive inhibition of body growth. The only apparent and consistent influence is that of patent ductus arteriosus which presumably resulted in a lessening of the normal supply of blood to the body tissues. A rapid increase in height was observed in the twin with patent ductus arteriosus following operative closure of the defect. The growth-inhibiting factor must therefore be considered an added reason for surgery, and the optimum time for operation is probably before the age of 11 years. DURANT.

Scherf, D., and Schlachman, M.: The Electrocardiographic Changes Caused by Hyperventilation. Am. J. M. Sc. 213:342 (March), 1947.

The influence of hyperventilation on the electrocardiogram was studied. In a majority of the cases a lowering of the R and of the T waves in Lead I was noted. These changes were independent of the presence of an alkaline shift in the blood serum and independent of the signs and symptoms of tetany. The changes were identical, whether the hyperventilation consisted of rapid and shallow breathing, rapid and deep breathing, or slow and deep breathing. They appeared as early as three minutes after the beginning of hyperventilation and returned to normal within ten minutes after hyperventilation had ceased. The changes were the same as those which appeared when the electrocardiogram was taken during forced inspiration.

It is concluded that the alterations are explained by positional changes of the heart. As long as a marked increase in heart rate was avoided and the respirations were not sufficiently

rapid and shallow to cause anoxia, no depression of the RS-T segment was observed following hyperventilation. The alteration of the RS-T segments and the T-wave changes which may be observed in some women with endocrine imbalance is not due to hyperventilation. DURANT.

Thill, C. J., and Meyer, O. O.: Experiences With Penicillin and Dicumarol in the Treatment of Subacute Bacterial Endocarditis. Am. J. M. Sc. 213:300 (March), 1947.

Of twenty-two patients with subacute bacterial endocarditis, thirteen received both penicillin and Dicumarol, and nine were given only penicillin. Despite the fact that the results were better in the group receiving combined therapy, the authors remain decidedly skeptical that anticoagulant therapy offers any advantages, and feel that it is unquestionable that anticoagulant therapy carries with it grave hazards in subacute bacterial endocarditis. Prolonged therapy, either with penicillin alone or combined with Dicumarol and persisting for a minimum of six weeks, gives decidedly better results than any other method. Sensitivity tests are of great value, since there is a good correlation between sensitivity and clinical response. It is of interest that five of the seven failures in this series occurred in patients who had received distinctly inadequate therapy before coming under observation, and this in spite of the fact that all but one of these had become subjectively and objectively improved under the original inadequate therapy. In one instance, it was found that penicillin given fourteen hours before and fifty-four hours after the extraction of a tooth, the dosage being 15,000 units every three hours, was inadequate to prevent the recurrence of subacute bacterial endocarditis in a patient whose disease had become arrested almost a year previously. DURANT.

Hodges, H. H., and Freeman, N. E.: Thrombophlebitis on the Medical Service of a General Hospital. Am. J. M. Sc. 213:226 (Feb.), 1947.

This report is based on ten instances of thrombophlebitis in the lower extremity observed in a General Hospital during a four-month period. Eight of these developed in patients with scrub typhus fever (an incidence of 5 per cent in 130 consecutive cases). Treatment, the authors believe, should be individualized depending on the location and extent of the lesion. When thrombophlebitis is confined to the calf veins, lumbar paravertebral sympathetic block was used with uniformly good results. This procedure probably tends to prevent central propagation of the thrombus, embolism did not occur, and patients were spared the prolonged disability which follows femoral vein ligation. Anticoagulants might help prevent propagation of the thrombosis, but their use is usually unnecessary, and is prohibited in the presence of lumbar sympathetic block because of the danger of retroperitoneal hemorrhage. Thrombophlebitis involving the calf and femoral veins was treated by proximal ligation. Sympathetic block was used only for relief of pain after ligation. In one case of calf vein thrombosis with extension into the femoral vein, paravertebral procaine block prior to femoral ligation was followed promptly by pulmonary embolism. Iliofemoral thrombophlebitis was treated with heparin, high ligation being inadvisable in these ill patients. The results were satisfactory. In addition to the specific measures all patients were treated with elevation of the extremity, compression bandage, bed exercises, and early mobilization. From their observations the authors believe that all cases of iliofemoral thrombophlebitis do not necessarily result from extension of a calf vein thrombosis; such a process may originate occasionally in the iliofemoral region. DURANT.

King, B. G., and Henson, M.: Electrocardiographic Changes in Fulminating Anoxia. J. Aviation Med. 18:3 (Feb.), 1947.

The authors investigated the rapidity with which electrocardiographic changes can occur in rapidly developing anoxia during altitude flights to obtain a better understanding of the mechanisms of rapidly deteriorating physiologic states, and to obtain information on the mechanisms underlying functional electrocardiographic changes. Special attention was given to the voltage and configuration of the P, QRS, and T deflections, S-T segment deviations, and durations of the P-R and Q-T intervals.

Anesthetized dogs were suddenly transferred from 100 per cent oxygen to 100 per cent helium or nitrogen. This procedure resulted in a most severe degree of anoxic anoxia which led to respiratory failure within 120 to 240 seconds. Cardiac failure occurred shortly thereafter, and resuscitative measures, applied four to five minutes after starting inhalation of the inert gas, failed in four of the nine cases in which remedial measures were attempted.

Records were taken from the first three standard leads during each minute of inhalation. The heart showed such marked changes in conduction, rhythm, or in origin of the beat, either before or shortly after the third minute of anoxia, that comparison of voltages, configurations, and intervals with control values was no longer warranted.

The most dramatic change during the period of co-ordinate activity was the increase in the potential of the T wave. The R wave decreased in voltage in two leads in seven of the eight dogs during exposure to helium and in seven of the eight during exposure to nitrogen. No significant or constant change in the voltage of the P wave was observed. A high take off of the T wave was observed in five dogs breathing helium and in four dogs breathing nitrogen. Slowing of the heart after the initial acceleration occurred during the first minute in a majority of the dogs, although the acceleration stage was observed as late as the third minute in a few instances. The P-R intervals were all within the normal range as long as there was co-ordinate activity of the heart. Changes in QRS interval were within normal limits; such small changes as did occur being about equally divided between increased and decreased duration.

Human subjects breathing air were exposed for brief periods to simulated altitudes of 25,000 and 35,000 feet. In some instances, successive recordings of the first three standard leads were made during the development of anoxia. In others, progressive changes were followed in Lead II.

There was a constant decrease in the voltage of the T wave in all of the eleven observations on seven subjects. Of the five subjects exposed to both altitudes, three showed the greater change at 35,000 feet and two at 25,000 feet. At the higher altitude changes were noted in ten seconds in four subjects, in thirty seconds in one subject, and in ninety seconds in one subject. Exposure to 25,000 feet resulted in changes in thirty to sixty seconds. At this altitude, transient increases in potential were noted in two cases after two and four minutes.

Changes in the R-wave potential were not consistent, but decrease in voltage occurred in four cases, with no change in five cases, and an initial increase of voltage with a return to the control value in two subjects. Small increases in the voltage of the P wave were seen in eight of the eleven trials. No significant changes in the P-R or the QRS intervals, or the S-T segment were noted.

The authors believe that the electrocardiographic changes which occur during brief exposure to anoxic anoxia are almost certainly attributable to functional changes and/or to shifts in the electrical axis of the heart rather than to permanent damage of the cardiac muscle. BELLET.

Dry, T. J., Butt, H. R., and Scheifley, C. H.: The Effect of Oral Administration of Para-Aminobenzoic Acid on the Concentration of Salicylates in the Blood: Preliminary Report. Proc. Staff. Meet., Mayo Clin. 21:497 (Dec. 24), 1946.

The authors suggest that the action of salicylates in rheumatic fever may be more specific than has been recently supposed. It is known that rheumatic fever affects predominantly mesenchymal structures, the principal substrate of which is hyaluronic acid. The younger the tissue, the more readily will diffusion take place; and any agent capable of hydrolyzing hyaluronic acid increases this property.

The enzyme, hyaluronidase (derived from many strains of hemolytic types of streptococci and from extracts of umbilical cord and testes), is capable of just this action: it decreases the viscosity and favors the passage of liquids, exudates, and pathogenic tissues. When dyes are injected into the skin, the addition of hyaluronidase causes an increased diffusibility of these dyes, as demonstrated in both human beings and animals by Guerra. What is more impressive is that the extent of the spread is inhibited 57 to 66 per cent by the oral or intravenous administration of sodium salicylate, and that the degree of inhibition varies according to the dose of salicylate administered.

These observations are illuminating from the standpoint of the etiology and behavior of rheumatic fever when they are considered in the light of an enzyme system capable of producing

such profound and dramatic effects in special regions and tissues without actual direct bacterial invasion. Furthermore, the quantitative relationship which these reactions seem to bear to salicylate saturation cannot be without significance. If this is true, then the assurance of adequate quantities of salicylates in the blood must be of much importance, and may be directly related to those instances in which the therapeutic response is inadequate and in which relapses occur. It is in this connection that these authors introduced in this discussion the use of para-aminobenzoic acid.

The authors report a case in which they were unable to obtain a sufficiently high level of salicylates in the blood in spite of a liberal intake of salicylic acid, namely, 150 grains (10 Gm.), with an equal amount of sodium bicarbonate, per day. Following the simultaneous oral administration of para-aminobenzoic acid, in an initial dose of 4 Gm. followed by 2 Gm. every two hours around the clock, there resulted a steady increase in the salicylate level of the blood with a coincident dramatic clinical response.

In two control experiments involving healthy men these authors demonstrated that the content of salicylate in the blood obtained by a fixed daily dose of 10.6 Gm. of sodium salicylate with an equal amount of sodium bicarbonate increased considerably after the supplementary administration of para-aminobenzoic acid.

The authors conclude that salicylates and para-aminobenzoic acid appear to have a reciprocal effect in increasing their concentration in the blood when they are administered together orally. Additional studies are in progress to determine whether this phenomenon is dependent upon competitive excretion by the kidney or on some other metabolic effect. BELLET.

Kottke, F. J., Kubicek, W. G., and Laker, D. J.: Physical and Nervous Factors in Experimental Hypertension. Arch. Phys. Med. 28:146 (March), 1947.

The authors studied the effect of diathermy on the systemic blood pressure, renal blood flow, and glomerular filtration of patients with hypertension. The patients were treated with diathermy for two hours daily for two to five weeks. In none of them was there an appreciable decrease of blood pressure. During each diathermy period there was a slight fall of blood pressure but no greater than would be found during a similar rest period. Six determinations of renal blood flow were carried out on four patients during diathermy treatment. Two determinations were made on a patient with severe hypertension during treatment with diathermy. This subject had an abnormally low renal plasma flow. In the first experiment, with a heat input of 104 calories per hour, there was no appreciable change in renal plasma flow during diathermy. The blood pressure rose slightly, and the pulse rate increased considerably. In the second experiment, with a heat input of 43 calories per hour, the renal plasma flow tended to fall throughout the diathermy treatment.

In other experiments, short wave diathermy was administered to the kidney region or to the head. In one of the experiments, on a 37-year-old man with a moderate hypertension, diathermy to the back resulted in a marked decrease of renal blood flow. The renal blood flow fell to 50 per cent of the initial value.

In this series of cases, diathermy decreased the renal blood flow in normotensive and hypertensive patients. The systemic circulatory reflexes responded to heat by increasing cutaneous circulation and decreasing renal as well as splanchnic blood flow. Since diathermy decreased renal blood flow, it appears to be of no value, or even harmful, in treating hypertension. BELLET.

Gertler, M. M., and Yohalem, S. B.: The Effect of Atabrine on Auricular Fibrillation and Supraventricular Tachycardia in Man. J. Mt. Sinai Hosp. 13:323 (March-April), 1947.

This paper is presented as a preliminary report stressing the usefulness of atabrine in auricular fibrillation and paroxysmal supraventricular tachycardia as an alternative to quinidine.

The authors report a case of auricular fibrillation in a 55-year-old salesman who was admitted to the hospital with a temperature of 104.6 F., and a pulse of 80. No abnormalities were noted except for brawny, red, tender swelling of the left leg without cords, and the patient was treated for erysipelas of the leg. On the ninth day of hospitalization auricular fibrillation de-

veloped. Previous electrocardiograms had been abnormal. Two and half hours after the intramuscular administration of atabrine, there was a return of normal sinus rhythm.

The second case was an 88-year-old woman with nodal tachycardia who was admitted to the hospital in a semicomatose condition with a temperature of 100.6 F.; a pulse of 70; respirations, 30; and blood pressure 115/60. There were moist râles at the lung bases posteriorly, the heart was slightly enlarged, the heart sounds were well heard, and no murmurs or pathologic accentuations were present. Atabrine was administered intravenously and regular sinus rhythm was restored within forty-five seconds after the injection. The rhythm remained regular for two days at which time the patient died from the effects of diffuse carcinomatosis.

The authors feel that atabrine may have a distinct advantage over quinidine. In intramuscular doses of 0.4 Gm., atabrine reaches a blood level of 60 to 220 gamma per liter within one hour and falls to levels of 60 to 150 gamma per liter in three hours. The maximal effect, therefore, should occur early. Thus, in unselected cases of auricular fibrillation, one may know in three or four hours, instead of waiting five to ten as with quinidine, whether or not response is to be expected. In such instances, search for another drug such as digitalis may be begun earlier.

Atabrine should be used with caution unless one is completely familiar with its pharmacologic and physiologic properties, for the drug is not without toxicity. BELLET.

Kossberger, J.: Rheumatic Pneumonia. J. Pediat. 30:113 (Feb.), 1947.

Evidence that rheumatic disease is the result of reaction to foreign antigens has been accumulating for a number of years. Infection with an organism such as the *Streptococcus hemolyticus* produces sensitivity rather than immunity of cells in other parts of the body. If further infection by the antigen occurs, an allergic reaction ensues. Foreign antigens may also cause the production of antibodies and if antigen and antibody meet in vascular tissue, the resulting reaction may injure the previously sensitized endothelial cell of the capillaries. It has been shown that an antigen consisting of streptococci and renal tissue can cause the formation of auto-antibodies, which react with the antigen in glomeruli to produce glomerulonephritis. It is possible that exudative lesions in rheumatic fever are produced by a similar response in cardiac tissue and other mesenchymal structures. Pulmonary lesions in rheumatic fever may be due to focal endothelial cell injury with increased capillary permeability, and transudation of albuminous fluid into the alveoli, alveolar ducts, alveolar septa, and interlobar spaces.

In addition, there is diapedesis of erythrocytes into alveoli, infiltration of the alveolar walls, and rupture of the walls with alveolar coalescence and intra-alveolar hemorrhage. The original albuminous transudate may be pressed against the alveolar wall by intra-alveolar air tension and become a hyaline membrane lining the alveoli and bronchioles. Septal cells, or possibly basal cells of bronchiolar epithelium, proliferate to form a single or stratified layer of cuboidal cells lining the alveoli. The plugs of fibrinous exudate which fill the alveolar ducts and project into the alveolar spaces become organized and form "Masson Bodies." These bodies are said to be present in bronchiectasis, tuberculosis, pulmonary abscess, and many other conditions.

Two cases of rheumatic pneumonitis are reported in detail. One was a girl 7 years of age, and the other a boy, aged 9 years. Both had active rheumatic infection, developed congestive failure, and both died three weeks after admission. Histologic examination of the lungs showed many of the characteristic features described above. HAUB.

Book Reviews

WHAT YOU CAN DO FOR ANGINA PECTORIS AND CORONARY OCCLUSION. By Peter J. Steincrohn, M.D., F.A.C.P., Doubleday and Company, Inc., Garden City, N. Y., 1946. Price \$2.50. With 254 pages.

This is a sincere and highly successful attempt to talk to the patient in terms which cannot be misunderstood. With a few unimportant exceptions, the author's point of view can be heartily endorsed. Dr. Steincrohn is to be commended particularly for exploding several shabby old taboos. Most patients will profit from this book, and perhaps even enjoy it, but some will overlook the reassuring passages and become agitated by the fact that, after all, death is occasionally mentioned. Nothing but total insulation could ever protect such persons from emotional tailspins. It might be well, therefore, not to recommend this book indiscriminately to patients, but all physicians who deal with coronary artery disease should read it.

HORACE M. KORNIS.

CARDIOPATOLOGIA. By A. A. Michelazzi. Rosenberg & Sellier, Torino, Italy, 1947. With 469 pages and 85 figures.

This book attempts to simplify Cardiology so that the practitioner may understand its basic principles, reach a diagnosis, and treat a patient without the help of a specialist.

While the description of methods of study is oversimplified, to the point that no mention is made of the precordial leads in electrocardiography, reference to these is made in the discussion of various diseases. The physiologic views of the author are not up to date, as is proven by the admission of a "cardiac tonus", by the statement that adrenalin is the sympathetic mediator, and by the claim that only one valvular event is responsible for each heart sound. The modern classification of gallop rhythms is ignored by the author; they are not clearly differentiated from the splitting of the heart sounds caused by bundle branch block. The statement that the "opening snap" of the mitral valve has no diagnostic importance should be questioned. The statement that peripheral edema is nearly constant and severe in adhesive pericarditis is contradicted by common observations.

Some inexactitudes are probably misprints: for example, the statement that the cyanosis of pulmonary stenosis is due to hypertension of the lesser circulation. The importance of blood pressure for the practitioner is not sufficiently emphasized; the factors responsible for and causing variations of this dynamic element are not properly stressed. The only phonocardiographic tracing reproduced in the book was apparently recorded with obsolete apparatus. Otherwise, phonocardiography is disregarded and many important interpretations in the field of clinical auscultation, demonstrated by this method, are omitted.

A curious fact should be noted: the doses of many digitalis preparations are given in grains. As the apothecary system is unknown in Italy, it is hard to understand how a practitioner in Italy will be able to evaluate them.

It is the reviewer's opinion that many discussions about the mechanism of various clinical disturbances could be omitted. The purpose of the book is sound. A new attempt in this direction should be encouraged because of the importance that such a work may have for the general practitioner.

A. LUISADA.

LA VELOCITA DELLA COZZENTE DEL SANGUE NELLA TERAPIA. By T. Sessa, L. Cappelli, Bologna, Italy, 1943. With 70 pages and 14 figures.

This monograph discusses circulation time and its importance in diagnosis and treatment. Many methods are described but the arm-to-lung test is omitted. After a brief study of the physiologic and clinical conditions causing variations of circulation speed, the author discusses the importance of these tests in general practice.

The following chapter deals with the actions of different drugs on circulation time. Digitalis and strophanthus glycosides, metrazol, caffeine, atropine, quinidine, ergotamine, pilocarpine, adrenaline, sympamine, sympathol, paredrinol, amyl nitrite, nicotinamide, thyroxine, insulin, histamine, mercurial diuretics, morphine, and heparin are discussed. The effects of bleeding, blood transfusion, paracentesis, pneumothorax, pneumoperitoneum, and anesthesia are also discussed. Drugs and physical procedures are then divided into two classes, those accelerating and those slowing the rate of circulation.

A less verbose discussion and a clearer understanding of both the factors of circulation and the actions of drugs would have increased the value of this booklet. Still, it may be useful as a reference manual since it contains a considerable amount of data.

A. LUISADA.

Correspondence

TO THE EDITOR:

In a paper in the January, 1947, issue of the AMERICAN HEART JOURNAL (vol. 33, pp. 1 to 13) on "Electrocardiographic Studies in Rheumatic Heart Disease," Doctors First, Stickle, and Bayley employ criteria for the electrocardiographic diagnosis of ventricular hypertrophy which are open to considerable question. The authors state: "The electrocardiogram shows a prominent R at V_5 and V_6 which indicates left ventricular hypertrophy." Furthermore, they say, "Fig. 5 shows a prominent S at V_2 and V_3 which indicates left ventricular hypertrophy." It is true that in the precordial electrocardiogram characteristic of left ventricular hypertrophy the R wave is usually abnormally large in leads from the left side of the precordium (V_5 and V_6) and the R wave is small or absent and followed by a deep negative deflection in leads from the right side of the precordium (V_1 and V_2). However, other abnormalities are often observed. Wilson and associates (AM. HEART J. 27:19, 1944) have pointed out that the QRS interval is increased to .10 or .11 second and that the prominent R wave occurs abnormally late in the QRS interval in leads from the left side of the precordium (V_5 and V_6). This has been ascribed to the increased thickness of the left ventricular wall. In addition, both Wilson and associates and Goldberger (AM. HEART J. 28:621, 1944) have described inverted T waves along with depression of the RS-T segment in these same leads when the precordial electrocardiogram was characteristic of left ventricular hypertrophy. Applying these criteria to the tracings which are claimed to demonstrate left ventricular hypertrophy in this paper, very few can be considered representative.

Further, the authors base their diagnosis of combined right and left ventricular hypertrophy on the findings of a prominent R and S in Leads V_2 , V_3 , and V_4 from the right side of the precordium and a prominent R at V_5 and V_6 from the left side of the precordium. These changes cannot be considered characteristic of combined ventricular hypertrophy. It is believed that the presence of the left ventricular hypertrophy when combined with right ventricular hypertrophy may produce changes in the long axis of the heart resulting in normal axis or even right axis deviation. However, the precordial electrocardiogram will resemble that seen in isolated left ventricular hypertrophy. (Goldberger, E.: AM. HEART J. 28:621, 1944.) It is believed generally that it is difficult to determine the electrocardiographic presence of right ventricular hypertrophy when the precordial electrocardiogram is characteristic of left ventricular hypertrophy.

The questionable evidence of left ventricular hypertrophy presented in these electrocardiograms would seem to cast doubt upon the conclusion of these authors. "That left ventricular hypertrophy occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy," has not been proved convincingly by the data contained in this paper. It seems that a pathologic study of rheumatic heart disease with an attempt made to determine the ratio of the right and left ventricular weights would solve this problem better. Some of the other conclusions in this paper, based upon the electrocardiographic diagnosis of ventricular hypertrophy are open to question.

MARVIN SCHWARTZ, M.D.

University of Oregon Medical School
Department of Medicine
Division of Cardiovascular Disease
Portland, Oregon

The following is a reply to Dr. Schwartz' letter:

TO THE EDITOR:

The authors are aware of various points emphasized by Dr. Schwartz. He opens his communication with objection to the legend of Fig. 5. We feel that it is necessary to call his attention to Fig. 6 recorded from the same subject and to the fourth paragraph of the "Discussion" where we state, "Thus far, we have used the term hypertrophy when the R and S deflections in the precordial leads exceeded the standard offered by Wilson and associates.⁹⁻¹² It should be pointed out, however, that cardiac dilatation, which produces a closer proximity of the ventricular and the thoracic walls, may, by diminishing the distance from the exploring electrode to the accession wave, produce QRS deflections similar to those of hypertrophy. In subjects with electrocardiographic evidence of an initial increase in ventricular size and later a return to normal (Figs. 5 and 6), dilatation, rather than hypertrophy, probably predominates." Dr. Schwartz can have his choice.

With respect to the QRS interval: if Dr. Schwartz requires QRS intervals of .10 to .11 second for all curves on which he offers an electrocardiographic diagnosis of ventricular hypertrophy, there will be instances in which the latter will include intraventricular block; not to mention the fact that the majority of low-grade and moderate ventricular hypertrophies will be excluded arbitrarily, especially in children (with whom we were necessarily dealing).

With respect to the inverted T and deflection of the RS-T segment in subjects with left ventricular hypertrophy, these phenomena imply a more uniform duration (with respect to the normal) of the excited electrical state at the epicardial and the endocardial surfaces of the left ventricle, and it is true that this phenomena occurs relatively late in the course of hypertensive heart disease with pronounced hypertrophy of the left ventricle and often disappears quite rapidly following successful sympathectomy, but we fail to see its importance in connection with the present problem.

In an article entitled, "On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease" (Bayley, R. H.: *AM. HEART J.* 26:769, 1943), the phenomena were described by stating that the free wall of the left ventricle acts electrically as if it were chronically ischemic. Again, if Dr. Schwartz requires this type of primary T-wave change to establish a diagnosis of left ventricular hypertrophy, he will lower unnecessarily the instance of his diagnosis of hypertrophy.

With respect to combined hypertrophy of the right and of the left ventricles, there is no sound reason why "right ventricular hypertrophy plus left ventricular hypertrophy should produce multiple precordial-lead effects which are identical to those of isolated left ventricular hypertrophy," and we do not agree that such is the case. We do agree, however, that the problem is occasionally difficult, particularly in single electrocardiograms. With combined hypertrophy of the right and left ventricles, the abnormally great amplitude of R and the delay of the chief downstroke in unipolar leads from the right side of the electrical precordium have the same significance with respect to the anticipated effects for isolated left ventricular hypertrophy as they have with respect to the normal. The same reasoning applies to dilatation in relation to the amplitude of R.

We would have no objection to a revision of our conclusions to include, "Left ventricular hypertrophy and/or dilatation occurs more frequently as a result of rheumatic heart disease than does right ventricular hypertrophy and/or dilatation." We are of the opinion that the unipolar precordial electrocardiogram offers the only accurate picture of ventricular size and is the only means whereby right ventricle enlargement can be differentiated from left. With the use of serial teleroentgenograms and fluoroscopy, we have frequently observed the development of an increase in the overall size of the cardiac silhouette when a diagnosis of low-grade or moderate ventricular hypertrophy was apparent in the electrocardiogram. In most instances, the increase in size of the cardiac silhouette was not of sufficient magnitude to alter the cardiothoracic ratio

from the normal, and it follows that the diagnosis of cardiac hypertrophy is unlikely in the majority of these teleroentgenograms. Our conclusions are also supported by a corresponding decrease in the size of the cardiac silhouette when the electrocardiogram shows a return to the normal (as was the case in Figs. 5 and 6).

Finally, we have every reason to believe that, if it were possible to obtain pathologic material on patients who have, as a rule, many years yet to live, this material would support our conclusions. In fact, in the occasional and all too frequent instances when death occurs relatively early in the overall course of rheumatic disease, primarily as the result of chronic rheumatic cardiac invalidism due primarily to recurrent active rheumatic myocarditis, the pathologic material obtained has supported our electrocardiographic findings. We are convinced that the general impression which our article contradicts was primarily due to the study of pathologic materials obtained at the end stage of prolonged rheumatic disease which leads most commonly to the "button hole" mitral stenosis and to secondary chronic pulmonary fibrosis and, only after the development of the latter, to chronic pulmonary arterial hypertension and right ventricular hypertrophy. We are not convinced that a ratio of ventricular weights is practical or sound. Even if it were practical, a ratio of ventricular weights might lend false support to our argument because of the greater fluid and substance of rheumatic inflammation in the left ventricular walls as compared to that in the right.

R. H. BAYLEY, M.D.
SAFETY R. FIRST, M.D

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

OFFICERS

President
DR. ARLIE R. BARNES

Treasurer
SAMUEL HARRELL

President Elect
DR. TINSLEY R. HARRISON

Secretary
DR. HARRY E. UNGERLEIDER

Medical Director
DR. CHARLES A. R. CONNOR

Vice-President
DR. CARL J. WIGGERS

Executive Secretary
DR. H. M. MARVIN

BOARD OF DIRECTORS

*THOMAS I. PARKINSON, Chairman.....New York City
DR. EDGAR V. ALLEN.....Rochester, Minn.
*DR. E. COWLES ANDRUS.....Baltimore
*DR. ARLIE R. BARNES.....Rochester, Minn.
DR. WILLIAM H. BUNN.....Youngstown, Ohio
*DR. GEORGE E. BURCH.....New Orleans
*S. DEWITT CLOUGH.....Chicago
*COLGATE W. DARDEN, JR.....Charlottesville, Va.
*JUSTIN DART.....Los Angeles
DR. CLARENCE E. DE LA CHAPELLE.....New York City
DR. GEORGE K. FENN.....Chicago
DR. MORRIS FISHBEIN.....Chicago
RUDOLPH F. HAFFENREFFER.....Providence
*SAMUEL HARRELL.....Indianapolis
*DR. TINSLEY R. HARRISON.....Dallas
ALFRED C. HOWELL.....Bethel, Conn.
*DR. T. DUCKETT JONES.....Boston
DR. LOUIS N. KATZ.....Chicago

*Executive Committee.

DR. JOHN D. KEITH.....Toronto, Can.
DR. ROBERT L. KING.....Seattle
MRS. WENDELL KINNEY.....Los Angeles
DR. WILLIAM B. KOUNTZ.....St. Louis
DR. EUGENE M. LANDIS.....Boston
DR. ROBERT L. LEVY.....New York City
DR. H. M. MARVIN.....New Haven, Conn.
DR. THOMAS M. McMILLAN.....Philadelphia
*ROBERT L. MEHORNAY.....Kansas City, Mo.
*DR. IRVINE H. PAGE.....Cleveland
*DR. JOHN J. SAMPSON.....San Francisco
DR. HOWARD B. SPRAGUE.....Boston
DR. EUGENE A. STEAD, JR.....Durham, N. C.
DR. J. ROSS VEAL.....Washington, D. C.
DR. HARRY E. UNGERLEIDER.....New York City
DR. HOWARD F. WEST.....Los Angeles
DR. CARL J. WIGGERS.....Cleveland
*DR. IRVING S. WRIGHT.....New York City

ASSEMBLY

DR. EDGAR V. ALLEN.....Rochester, Minn.
JAMES ANDERSON.....Philadelphia
DR. E. COWLES ANDRUS.....Baltimore
DR. GRAHAM ASHER.....Kansas City, Mo.
DR. ARLIE R. BARNES.....Rochester, Minn.
DR. EMMET B. BAY.....Chicago
DR. ALFRED BLALOCK.....Baltimore
ALVA BRADLEY.....Cleveland
EARLE BROWN.....Minneapolis
DR. LEWIS T. BULLOCK.....Los Angeles
DR. WILLIAM H. BUNN.....Youngstown, Ohio
DR. GEORGE E. BURCH.....New Orleans
DR. EDWARD W. CANNADY.....East St. Louis, Ill.
HARRY C. CARR.....Philadelphia
DR. FRANCIS L. CHAMBERLAIN.....San Francisco
PAUL F. CLARK.....Boston
S. DEWITT CLOUGH.....Chicago
DR. WARREN B. COOKSEY.....Detroit
CHANING H. COX.....Boston
JAMES A. CUNNINGHAM.....Chicago
COLGATE W. DARDEN, JR.....Charlottesville, Va.
JUSTIN DART.....Los Angeles
DR. CLARENCE E. DE LA CHAPELLE.....New York City
DR. GEZA DE TAKATS.....Chicago
DR. FRANCIS R. DIEUAIDE.....New York City
DR. HARVEY M. EWING.....Montclair, N. J.
DR. GEORGE K. FENN.....Chicago
RICHARD J. FINNEGAN.....Chicago
DR. MORRIS FISHBEIN.....Chicago
DR. NORMAN E. FREEMAN.....San Francisco
ARTEMUS L. GATES.....New York City
SAMUEL GOLDWYN.....Los Angeles
A. E. GRAUER.....Vancouver, B. C., Can.
DR. JAMES A. GREENE.....Houston
RUDOLPH F. HAFFENREFFER.....Providence
SAMUEL HARRELL.....Indianapolis
RICHARD F. HARRISON.....Syracuse, N. Y.
DR. TINSLEY R. HARRISON.....Dallas
DR. JOHN HEPBURN.....Toronto, Can.
DR. GEORGE R. HERRMANN.....Galveston
DR. J. G. FRED HISS.....Syracuse, N. Y.
ALFRED C. HOWELL.....Bethel, Conn.
DR. W. C. HUEPER.....New York City
COLEMAN JENNINGS.....Washington, D. C.
DR. T. DUCKETT JONES.....Boston
DR. ALBERT D. KAISER.....Rochester, N. Y.
DR. LOUIS N. KATZ.....Chicago
SAMUEL H. KAUFFMANN.....Washington, D. C.
DR. JEROME G. KAUFMAN.....Newark, N. J.
DR. JOHN D. KEITH.....Toronto, Can.
DR. ROBERT L. KING.....Seattle
MRS. WENDELL KINNEY.....Los Angeles
DR. WILLIAM B. KOUNTZ.....St. Louis
DR. CHESTER M. KURTZ.....Madison, Wis.
DR. EUGENE M. LANDIS.....Boston

DR. BERNARD W. LEONARD.....Washington, D. C.
DR. ROBERT L. LEVY.....New York City
CLARE BOOTHE LUCE.....Ridgefield, Conn.
DR. HAROLD C. LUETH.....Omaha
RUTH E. LYNCH.....Los Angeles
DR. LOUIS E. MARTIN.....Los Angeles
DR. H. M. MARVIN.....New Haven, Conn.
DR. EDWIN P. MAYNARD, JR.....Brooklyn
DR. SAMUEL J. MCCLENDON.....San Diego
ALFRED J. MCCOSKER.....New York City
DR. HUGH MCCULLOCK.....St. Louis
DR. JOHNSON MCGUIRE.....Cincinnati
DR. THOMAS M. McMILLAN.....Philadelphia
ROBERT L. MEHORNAY.....Kansas City, Mo.
DR. J. ROSCOE MILLER.....Chicago
RICHARD M. MOSS.....Belleville, Ill.
DR. E. STERLING NICHOL.....Miami
DR. FRANKLIN R. NUZUM.....Santa Barbara, Calif.
DR. IRVINE H. PAGE.....Cleveland
THOMAS I. PARKINSON.....New York City
DR. MYRON PRINZMETAL.....Los Angeles
DR. SAMUEL PROGER.....Boston
DR. DICKINSON W. RICHARDS, JR.....New York City
DR. HAROLD H. ROSENBLUM.....San Francisco
DR. PHILIP ROSENBLUM.....Chicago
DR. HOMER P. RUSH.....Portland, Ore.
DR. JOHN J. SAMPSON.....San Francisco
DR. FRANCIS T. SCHWENTKER.....Baltimore
DR. HAROLD N. SEGALL.....Montreal, Can.
DR. ARTHUR SELZER.....San Francisco
DR. M. J. SHAPIRO.....Minneapolis
DR. HOWARD B. SPRAGUE.....Boston
DR. ISAAC STARR.....Philadelphia
HAROLD E. STASSEN.....St. Paul
DR. EUGENE A. STEAD, JR.....Durham, N. C.
DR. ERNEST L. STEBBINS.....Baltimore
DR. WILLIAM D. STROUD.....Philadelphia
DR. HOMER F. SWIFT.....New York City
DR. ALEXANDER W. TERRELL.....Dallas
DR. WILLIAM P. THOMPSON.....Los Angeles
DR. HARRY E. UNGERLEIDER.....New York City
DR. J. ROSS VEAL.....Washington, D. C.
DR. LOUIS E. VIKO.....Salt Lake City
DR. MAURICE VISSCHER.....Minneapolis
JOE E. WERTHAN.....Nashville
DR. HOWARD F. WEST.....Los Angeles
DR. PAUL D. WHITE.....Boston
CARL WHITMORE.....New York City
DR. CARL J. WIGGERS.....Cleveland
DR. FRANK N. WILSON.....Ann Arbor
DR. J. EDWIN WOOD, JR.....Charlottesville, Va.
GUS S. WORTHAM.....Houston
DR. IRVING S. WRIGHT.....New York City
J. D. ZELLERBACH.....San Francisco

MEMBERSHIP

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members resident in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....	\$ 2.50	Contributing Membership.....	\$25.00
Journal Membership.....	\$10.00	Patron Membership.....	\$50.00 or more
The dues of the local Heart Associations are added to these.			

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*.

Journal Membership includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the AMERICAN HEART JOURNAL through the publishers does not provide for membership in the American Heart Association.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.



American Heart Journal

VOL. 34

SEPTEMBER, 1947

No. 3

Original Communications

PHYSIOLOGIC CHANGES IN THE CIRCULATION DURING AND AFTER OBSTETRIC LABOR

ELLEN BROWN, M.D., JOHN J. SAMPSON, M.D., EDWIN O. WHEELER, M.D.,
BENJAMIN F. GUNDELFINGER, M.D., AND JOSEPH E. GIAN SIRACUSA, M.D.
SAN FRANCISCO, CALIF.

THE physiologic changes in the circulation which accompany and follow immediately after obstetric labor have not been studied in detail, although in terms of fatality and congestive failure the early puerperium is apparently the most critical period for patients with serious heart disease.^{1,2,3} In attempting to explain post-partum circulatory failure, two questions arise: (a) how important is the load imposed on the heart by the work of labor, and (b) what are the effects on the circulation of emptying the uterus, whether by cesarean section or by active labor?

The first question has been answered by the results of oxygen consumption studies⁴ which showed that the work of labor is variable but often severe. For example, work may be performed which is equivalent to climbing a seven-foot flight of stairs once every three minutes during a labor lasting twelve hours. Furthermore, the "oxygen debt" incurred during a long and hard second stage may not be repaid for over an hour after delivery. The changes in pulse and respiratory rate which occur during labor^{5,6} reflect the same situation. Work of this severity might be expected to precipitate failure of a functionally inadequate heart.

On the other hand, there is statistical evidence to show that emptying the uterus may in itself impose a burden on the heart. In patients with serious heart disease, deaths from congestive failure occur with equal or greater frequency

From the Divisions of Medicine, and Obstetrics and Gynecology, University of California Medical School.

Presented in part at the Second Inter-American Congress of Cardiology, Mexico, D. F., Oct. 5-12, 1946.

Received for publication Jan. 18, 1947.

following cesarean section, where the work of labor is excluded, than following vaginal delivery.^{10,7,8}

The effects of delivery on the circulation were studied by means of serial observations of several functions on individual patients, a method previously employed in investigating circulatory changes in pregnancy prior to labor.⁹⁻¹¹ Observations were made of heart rate, arterial and venous blood pressure, vital capacity, circulation time, plasma volume, and venous hematocrit at frequent intervals during labor and the early puerperium. In view of evidence presented by Burwell and co-workers^{12,13} to suggest that the pregnant uterus functions as an arteriovenous shunt of important proportions, acute changes were looked for which might indicate occlusion of such a shunt at delivery.¹⁴⁻¹⁸ The changes which were observed in normal patients and in three patients with heart disease, only one of whom was threatened by decompensation, were not sufficiently consistent to demonstrate the relative importance of (a) occlusion of a vascular shunt, (b) exercise, or (c) other factors in precipitating cardiac failure after delivery.

CLINICAL MATERIAL AND GENERAL PROCEDURE

Complete studies were made on thirteen normal and three cardiac patients who had uncomplicated vaginal deliveries and on two normal patients delivered by cesarean section without trial of labor. As soon as possible after the onset of labor, observations were made of pulse rate, blood pressure, venous pressure, vital capacity, circulation time, plasma volume, and hematocrit. These were repeated at two hours, six to twelve hours, twelve to thirty-six hours, two to three days, and four to eleven days after delivery. Two normal patients and one with heart disease delivered by the vaginal route and three normal patients delivered by cesarean section were studied in the same way except that plasma volume, hematocrit, and circulation time were not determined. Observations of pulse rate, blood pressure, and venous pressure were made at the usual times on nine patients who were delivered uneventfully by the vaginal route, but from whom oxytocic drugs were withheld until their need was evident, after which the effects of administration of these drugs were noted.

The patients were recumbent during all observations, and were in the fasting state except during the first twelve to twenty-four hours, during which a fat-free diet was given to ensure clear plasma. Records of fluid intake and output and of weight were kept as completely as possible. Labor was not extremely severe or prolonged in any patient, and blood losses, which were either measured or carefully estimated, were slight or moderate.

Most of the patients received barbiturates early in labor and inhalations of nitrous oxide-oxygen mixtures during pains in the second stage of labor. Two patients had caudal injections of metycaine, one pudendal, and one paravertebral nerve block. Local anesthesia was used for one cesarean section, and nitrous oxide-oxygen with ether or cyclopropane for the others. Following vaginal delivery, all patients received 1 c.c. of pituitrin or pitocin and 0.02 mg. of ergotrate (ergonovine maleate) intramuscularly, followed by 0.02 mg. of ergotrate orally every four hours for five doses, unless these drugs were specifi-

cally withheld. Following cesarean section, the initial .02 mg. of ergotrate was given intravenously.

METHODS

1. *Venous Pressure*.—The method of Moritz and von Tabora¹⁹ was used, the zero point being placed 5 cm. dorsal to the angle of Louis. Care was taken to obtain complete muscular relaxation and to avoid obstruction of the vein by postural distortion, muscular contraction, or the weight of the breast. The presence of suitable conditions was indicated by free motion of the column of fluid with respiratory excursions. The first few readings made after insertion of the needle usually indicated a gradual fall in pressure, suggesting that muscular contractions or spasm of the vein occurred initially as a response to pain. After a constant low level was reached, repeated readings were usually identical and this final low pressure was recorded.

2. *Vital Capacity*.—This was measured in the supine position with a water spirometer. The best result of three good efforts was recorded.

3. *Circulation Time*.—Arm-to-tongue time was determined by the method of Winternitz, Deutsch, and Brüll,²⁰ using 3 c.c. of 20 per cent decholin.

4. *Hematocrit*.—Venous blood was collected without stasis at the beginning and end of each determination of plasma volume, a 1.4 per cent solution of potassium oxalate was added, and the specimen centrifuged for thirty minutes at 3,000 revolutions per minute. The average of each pair of readings was used.

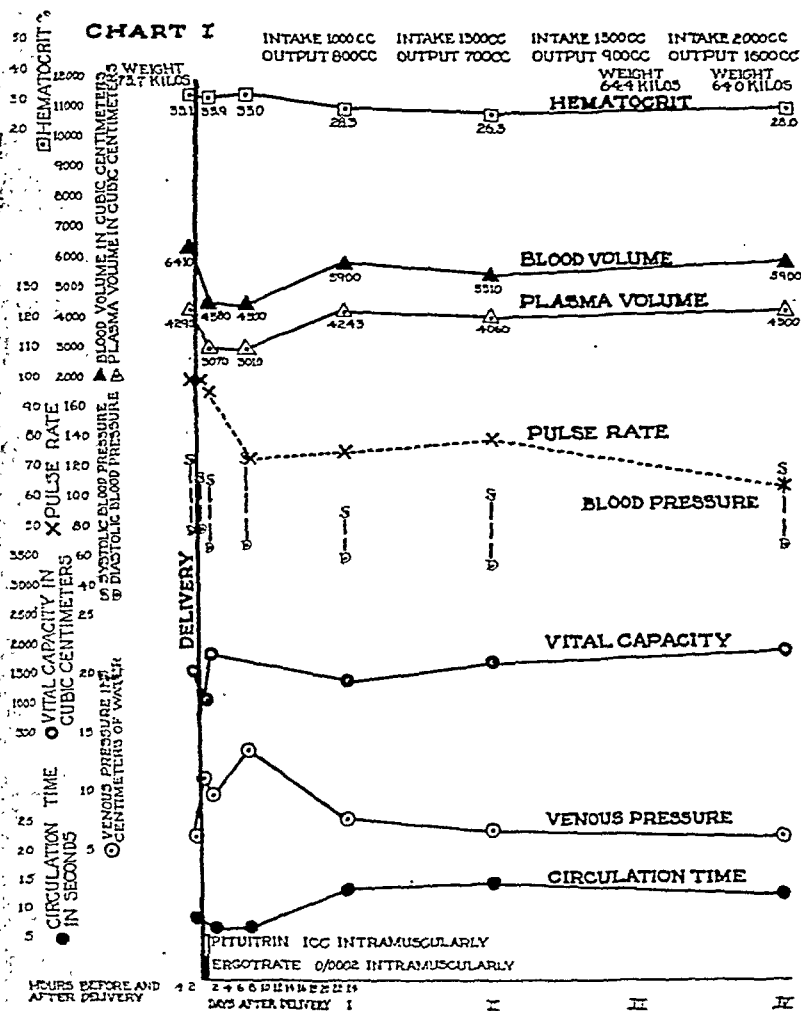
5. *Plasma and Blood Volume*.—Plasma volume was determined by the method of Gibson and Evans,²¹ using the Evelyn photoelectric colorimeter.²² Six c.c. of 2 per cent T-1824 were injected for the first determination and from 2 to 6 c.c. for subsequent determinations. Blood samples were collected nine, twelve, and fifteen minutes after injection of the dye. Gross evidence of hemolysis was rarely seen, and if so, the specimens were discarded.

Difficulty was encountered in calculating plasma volumes from the data because of large variations in the slopes of the T-1824 time-concentration curves. In thirteen of the total of 103 determinations, the optical density of the fifteen-minute sample was less than that of the nine-minute sample of serum by an amount equivalent to 20 per cent or more of the plasma volume. This may have been due to (a) delayed mixing of the dye, or (b) loss of dye and plasma from the blood stream during the time in which samples were collected.²³ The results of of these thirteen determinations were discarded as technically unsatisfactory although they were of some interest in view of the possibility that considerable volumes of stagnant blood may be present in the legs, pelvis, or other vascular reservoirs about the time of delivery.¹² Under such circumstances, mixing of the dye might be expected to be abnormal.

In the remaining determinations, the difference in optical density between the first and last samples represented less than 10 per cent of the calculated plasma volume, but because satisfactory disappearance slopes could be plotted in only half of them, the readings of the nine-, twelve-, and fifteen-minute samples were

averaged. The necessity for making repeated determinations of plasma volume at intervals of only a few hours may have led to errors in the use of the photoelectric colorimeter because of the presence of residual dye in the control samples of serum.²³ Technical errors in administering the dye are apt to give high values for plasma volume with this method, but because suitable precautions were taken to avoid losses of dye, it seems unlikely that the extremely high values obtained in some of these experiments could have been due to such errors.

The total volume of circulating blood was calculated indirectly from plasma volume on the basis of the venous hematocrit. The results were only approximate because (a) the accuracy of the determinations of plasma volume was probably no better than 10 to 20 per cent, and (b) the relation between venous hematocrit and total body hematocrit was an unknown and, perhaps, variable factor.



CASE XX NORMAL HEART VAGINAL DELIVERY
II. D.U. PRIMIPARA AGE 38 U96726

Height 168cm Usual weight 70.5K

Predicted blood volume 4150cc

Hours of labor 25½

Mid-forceps, R.O.P.

Fetal weight 3620gm

Blood loss 400cc

Analgesia: Caudal, nitrous oxide

Chart I.

RESULTS

The results of each study were plotted as illustrated in Charts I to IV. A fairly typical series of observations on a normal patient delivered by the vaginal route is shown in Chart I. Observations on a patient delivered by

cesarean section (Chart II) were not strikingly different except that the venous pressure remained elevated for a shorter time after delivery than occurred in the case of vaginal delivery, and the pulse rate was increased postoperatively. Chart III illustrates the course of a patient with inactive rheumatic heart disease, free aortic regurgitation, and moderate cardiac enlargement, whose functional capacity was only slightly limited prior to pregnancy and who progressed uneventfully through pregnancy and delivery. Except for high pulse pressure and

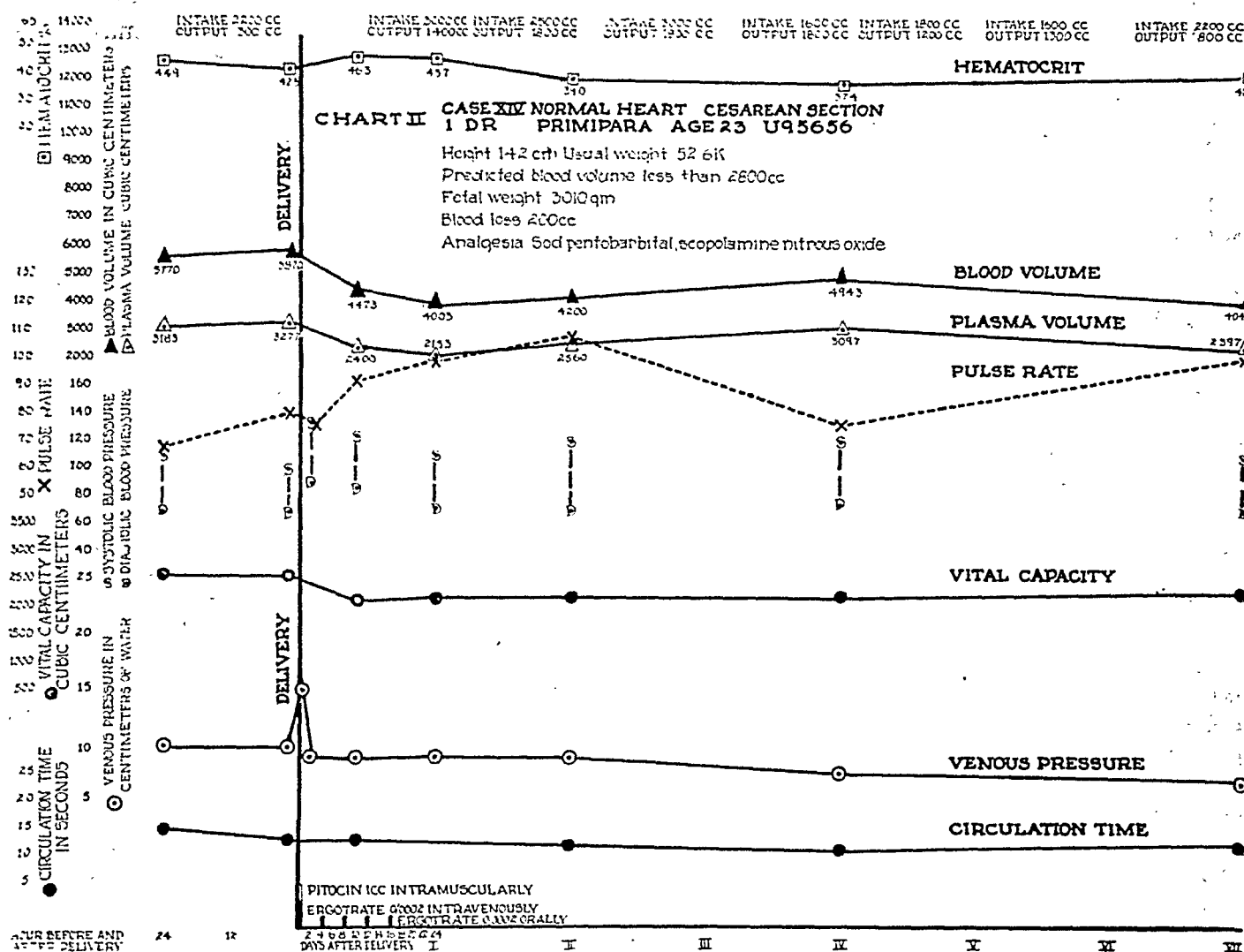


Chart II.

slightly accelerated pulse rate, this patient's course could not be differentiated from that of a normal individual by inspection of the chart. In Chart IV is shown the course of a patient with subacute bacterial endocarditis who was followed for several months before delivery. The large fluctuations of blood volume were attributed to marked wasting and anemia which developed between the March and April observations, and to the onset of left ventricular failure just prior to delivery. Basal lung râles were heard two hours after delivery and on the second post-partum day. The most striking features of the chart are the unusually prompt and extreme rise of venous pressure and the sharp drop in

pulse rate immediately post partum, even though the remainder of the patient's course was characterized by marked tachycardia.

For purposes of comparison, the changes taking place in individual functions were analyzed separately.

1. *Pulse Rate.*—Prompt slowing of the heart rate, which is the usual occurrence following occlusion of arteriovenous fistulas, did not appear regularly after deliveries involving active labor. A decrease of 10 beats or more per minute

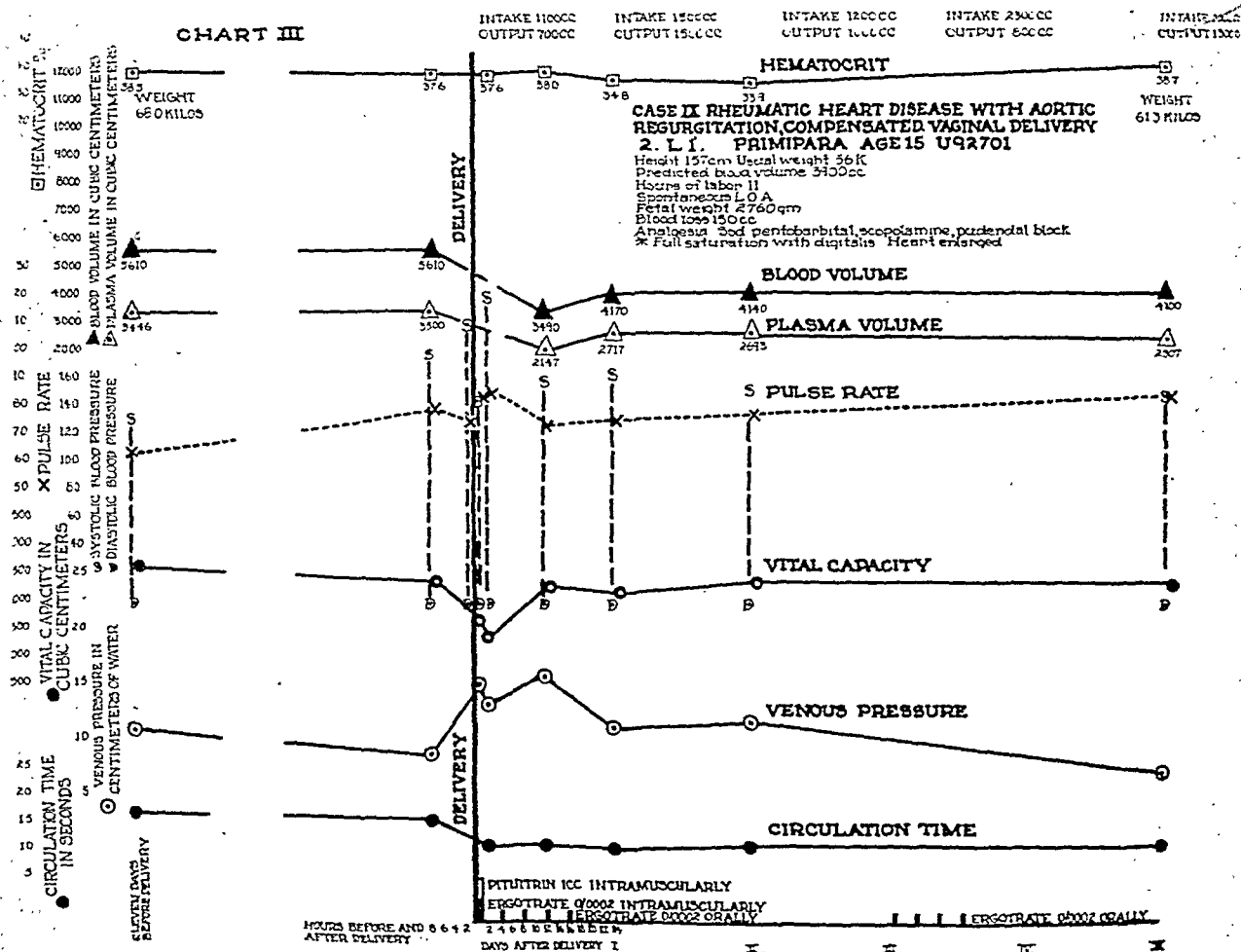


Chart III.

was observed at thirty minutes in only seven out of twenty-three and at two hours in only eleven out of twenty-four normal patients having vaginal deliveries. Significant decreases in pulse rate occurred even less frequently among the patients who received no oxytocic drugs than in those receiving the usual rations.²⁴ When delivery was not preceded by the work of labor, a post-partum decrease in pulse rate occurred more frequently. In three of the four cases delivered by cesarean section, the pulse rate had decreased more than 10 beats per minute by thirty minutes after removal of the fetus. It was possible to obtain counts just before and after removal of the fetus in only two of these cases. In one, the

rate decreased 20 beats (local anesthesia), and in one it increased 8 beats per minute (inhalation anesthesia).

2. *Blood Pressure.*—A post-partum increase in diastolic blood pressure would have been evidence to support the shunt hypothesis, but neither diastolic nor systolic pressure was affected regularly by delivery. At thirty minutes after delivery, there was an increase in diastolic pressure of 5 mm. Hg or more in only eight out of twenty-three, and at two hours, in only four out of twenty-four

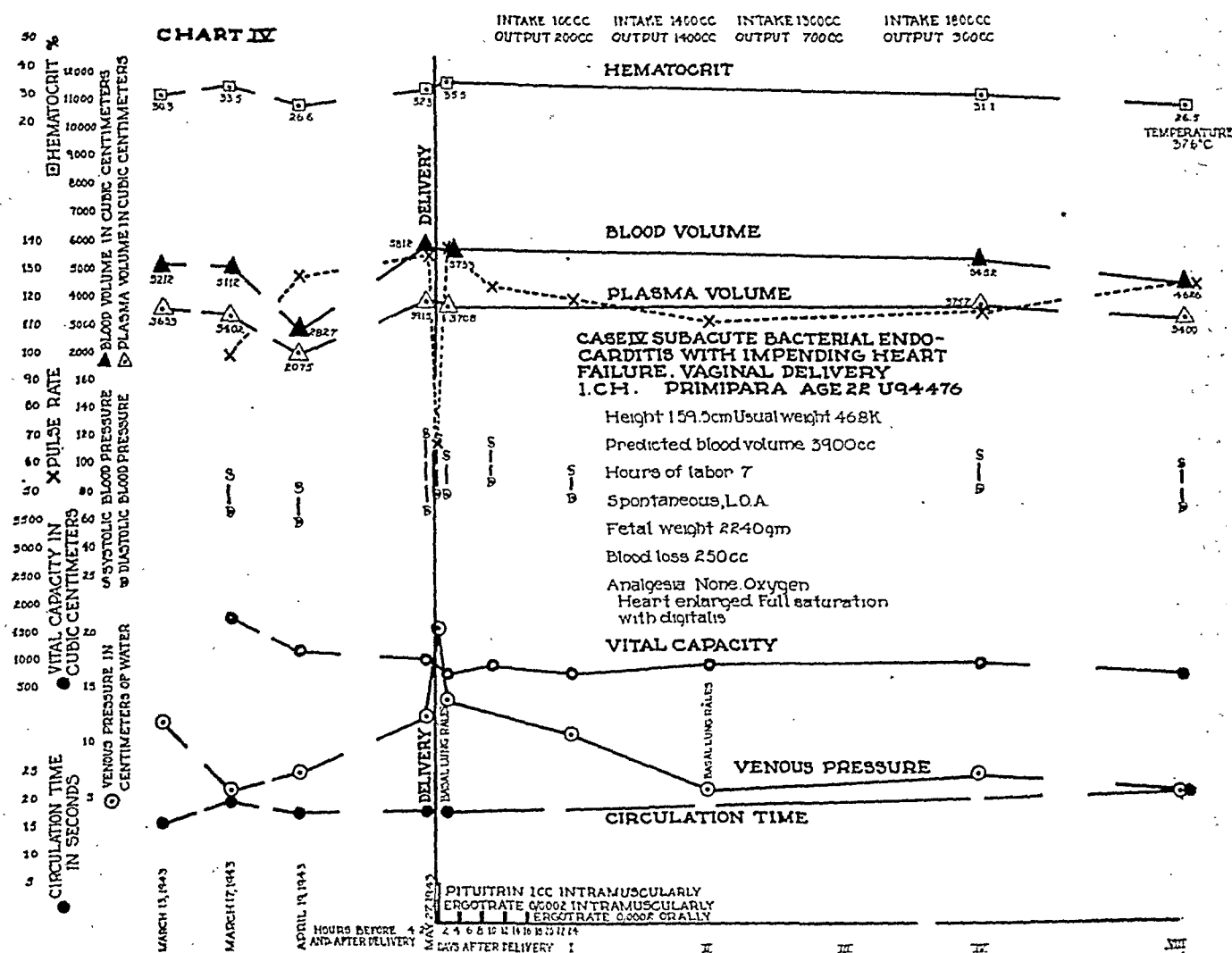


Chart IV.

normal patients delivered by the vaginal route. After cesarean section, diastolic pressure was increased by the same amount in one out of three patients at thirty minutes, and in three out of four at two hours.

3. *Venous Pressure.*—Among the normal patients who had vaginal deliveries, the venous pressures found during the first stage of labor were below the normal limit of 12 cm. H₂O, or slightly elevated (Table I). In the second stage, all the pressures which were measured between pains were within normal limits,

TABLE I. VENOUS PRESSURE IN CENTIMETERS OF WATER BEFORE AND AFTER DELIVERY

	BEFORE DELIVERY		AFTER DELIVERY					
	STAGE I	STAGE II	30 MINUTES	2 HOURS	6-12 HOURS	12-36 HOURS	2-3 DAYS	4-11 DAYS
Vaginal deliveries of normal patients with oxytocic drugs								
1 (Ol.)	6.5	5.5	14.0*	13.5*	13.5*	7.0	10.5	8.5
2 (Sc.)	9.3	8.5	10.0*	11.0*	12.0*	13.0	12.0	12.5
3 (To.)	8.7	—	15.0*	22.0*	8.5*	—	7.5	8.5
4 (Bu.)	10.5	—	9.0*	15.0*	11.5*	10.0*	8.5	6.5
5 (Fr.)	8.0	9.0	8.0*	17.0*	11.7*	11.5	11.0	17.5*
6 (Za.)	13.0	—	13.5*	19.0*	24.0*	22.0*	16.0	9.5
7 (St.)	12.5	—	15.5*	19.5*	18.3*	17.5	10.0	10.5
8 (Ny.)	7.8	7.4	15.5*	14.0*	12.0*	6.2	6.0	7.5
9 (Cl.)	12.5	—	—	17.0*	14.0*	14.5	13.0	12.5*
10 (Wa.)	8.0	8.0	13.0*	12.0*	10.7*	6.5	—	6.8
11 (Du.)	6.5	10.5	11.3*	10.0*	13.8*	8.0	7.0	6.5
12 (Ba., L.)	9.5	—	10.8*	12.3*	11.7*	14.0*	11.3	10.5
13 (Sa.)	9.0	—	13.5*	24.0*	19.0*	11.0	11.5	9.0
14 (Ba., J.)	10.5	—	7.5*	19.0*	25.5*	16.0*	11.0	10.0
15 (Vi.)	8.0	—	8.8*	10.5*	11.5*	8.3	7.2	9.5

*Ergotrate taken within four hours.

Vaginal deliveries of normal patients without oxytocic drugs	1 (Os.)	11.5	—	8.0	8.5	9.5	8.7	9.0	9.0
	2 (Jo.)	10.0	10.0	9.5	10.5	8.8	10.8	9.0	8.0
	3 (Cov.)	5.0	—	5.8	6.0	6.0	7.3	7.3	7.0
	4 (Si.)	5.5	—	7.8	8.8	8.0	7.3	8.3	6.8
	5 (El.)	9.8	—	9.3	8.8	7.5	8.0	8.0	8.5
	6 (Ma.)	14.0	—	8.5	9.3	9.0	8.0	—	—
	7 (Dr.)	8.5	—	9.5	8.5	11.5	11.0	8.5	—
	8 (Si.)	12.0	—	13.0	11.5	13.0	12.8	10.5	—
	9 (Wh.)	10.3	—	10.0	7.5	11.5	8.5	—	—
Vaginal deliveries of patients with heart disease with oxytocic drugs	1 (Ch.)	12.5	—	20.5*	14.0*	—	11.0	6.0	5.8
	2 (Li.)	9.0	—	15.2*	13.5*	16.0*	11.5	12.0	7.5
	3 (Cog.)	11.2	10.0	11.2*	16.0*	12.5*	9.5	9.2	10.0
	4 (Gr.)	9.0	14.0	14.0*	20.0*	17.0*	11.8	8.5	8.5
Cesarean sections of normal patients with oxytocic drugs	BEFORE OPERATION								
	1 (Dr.)	9.8	15.0*	9.5*	8.9*	9.0	9.0	9.0	6.8
	2 (Cop.)	9.5	20.5*	8.0*	14.0*	9.5*	9.5*	7.8	—
	3 (Cr.)	9.5	16.0*	12.5*	12.5*	10.5	10.5	10.5	9.3
	4 (Re.)	7.5	18.0*	14.0*	13.0*	12.0*	12.0*	11.0*	11.0
	5 (Wa.)	10.5	15.5*	17.0*	7.5*	10.5	10.5	13.0	9.5

*Ergotrate taken within four hours.

although very high pressures were found on a few occasions when measurements were made during uterine contractions.²⁵

In every normal patient who received oxytocic drugs, a rise of venous pressure occurred within two hours after delivery, the pressure reaching a level of 12 cm. water or above in twelve out of fifteen instances. In patients with abnormal hearts similar changes occurred, the elevation being higher and more prolonged in the one patient (*Ch.*) with cardiac failure. Fig. 1 illustrates the serial changes in venous pressure which occurred in individual patients. The

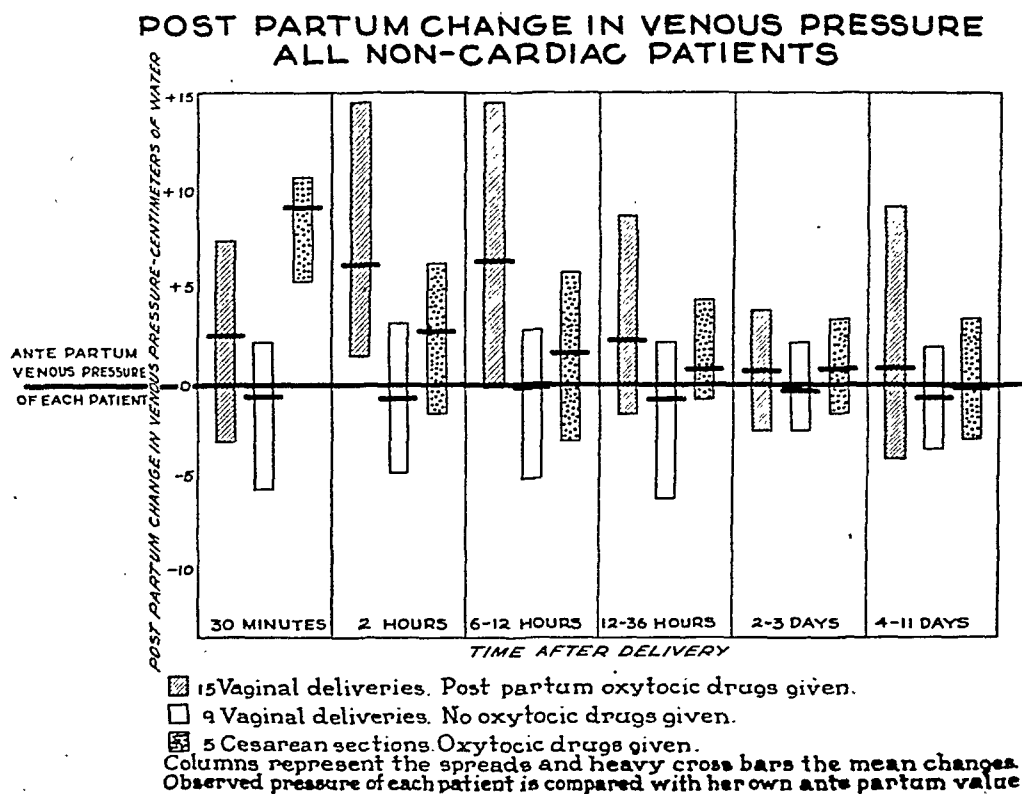


Fig. 1.

shaded columns representing normal vaginal deliveries show that at two hours after delivery, every patient had had a rise of venous pressure, the mean increase being 6.4 cm. water. The elevation was still present six to twelve hours after delivery but in most cases the venous pressure had returned to the ante-partum level by the second or third post-partum day.

To determine whether or not the work of labor was responsible for this rise of venous pressure, detailed studies were made of the changes in venous pressure following cesarean section. After delivery of the fetus there was a uniform increase in venous pressure, which was more immediate and more extreme but of shorter duration than that observed after vaginal deliveries (Table I, Fig. 1). Measurements of venous pressure were made during four abdominal deliveries by attaching the manometer through a three-way stopcock to a slow intravenous

drip of saline so that the infusion could be interrupted and pressures determined every few minutes. Patient *Cr.*, who received local anesthesia, showed a rise of pressure from 12.5 to 18.0 cm. within five minutes, and patient *Re.*, who had received general anesthesia, showed a rise from 14.8 to 18.0 cm. within three minutes after removal of the fetus. In the other two patients, the results were complicated by the effects of inhalation anesthesia.

The post-partum rise of venous pressure was therefore not caused by the work of labor. It seemed possible that the action of oxytocic drugs might be responsible because: (a) the elevations of pressure appeared earlier and were more marked when ergotrate had been given intravenously, and (b) the high pressures found after vaginal delivery were usually coincident with the recent administration of ergotrate. (Pressures measured within four hours of such medication are identified in Table I by means of asterisks.) It was found, moreover, that when the usual ratios of ergotrate and pituitary preparations were not given at the time of delivery, there was no post-partum rise of venous pressure (Table I, Fig. 1).

The effects of administration of oxytocic drugs later in the puerperium were studied in the nine patients from whom they had been withheld at the time of delivery. The usual doses of pituitrin had no perceptible effect on venous pressure, pulse, or blood pressure on two occasions. The results of ergotrate administration are summarized in Table II. When this was given orally in repeated doses, a significant elevation of venous pressure was present as late as eight to twenty-two hours after the beginning of treatment, but when an intramuscular dose accompanied the first of a similar series of oral doses, the elevations of venous pressure which occurred early were not sustained. Finally, when ergotrate was given to nonpuerperal hospital patients, both women and men, increases in venous pressure of 2.0 cm. H₂O or more occurred within thirty minutes to two hours after injection in four out of seven instances (Table II). These results appeared to confirm the suspicion that the administration of ergotrate was responsible for the rise of venous pressure which was usually observed post partum, and suggested that this effect might be the combined result of (a) auto-transfusion caused by contraction of the uterus,²⁶ and (b) decreased capacity of the vascular reservoir.

4. *Vital Capacity.*—The results obtained during labor and especially within twelve hours after delivery appeared to be related to the general state of the patient as evidenced by such factors as fatigue, preoccupation, and drowsiness, although cooperation was generally good. As compared with the values observed during labor, seven of thirteen normal patients delivered by the vaginal route showed decreases of between 100 and 900 c.c., while five showed increases of 150 to 500 c.c. at the two-hour observation. In one, no change was observed. By the time of the final observation at four to eleven days after delivery, nine out of twelve showed increases of 100 to 1,000 c.c. and three showed decreases amounting to between 100 and 250 cubic centimeters.

5. *Circulation Time.*—Before delivery, arm-to-tongue circulation time in the thirteen normal patients having vaginal deliveries varied between 9.0 and

TABLE II. CHANGES IN VENOUS PRESSURE FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION OF ERGONOVINE MALEATE

	DAYS AFTER DELIVERY	RESTING VENOUS PRESSURE (CM. H ₂ O)	ROUTE OF ADMINISTRATION*	NUMBER OF DOSES†	CHANGE IN VENOUS PRESSURE 30 MINUTES TO 2 HOURS AFTER INITIAL DOSE (CM. H ₂ O)	CHANGE IN VENOUS PRESSURE 8½ TO 22 HOURS AFTER INITIAL DOSE (CM. H ₂ O)
Puerperal patients						
1 (Os.)	8	9.0	Oral	3	-0.8	+2.8
2 (Jo.)	4	9.0	Oral	2	—	+3.0
3 (Co.)	6	7.5	Oral	3	+5.0	+5.5
4 (Si.)	4	6.8	Oral	5	—	+6.0
5 (El.)	3	8.0	Oral Intramuscular	5 1	+3.0	+1.0
6 (Ma.)	2	7.8	Oral Intramuscular	1 1	+4.0	—
7 (Sl.)	1 (20 hours)	12.8	Oral Intramuscular	4 1	+4.3	-2.3

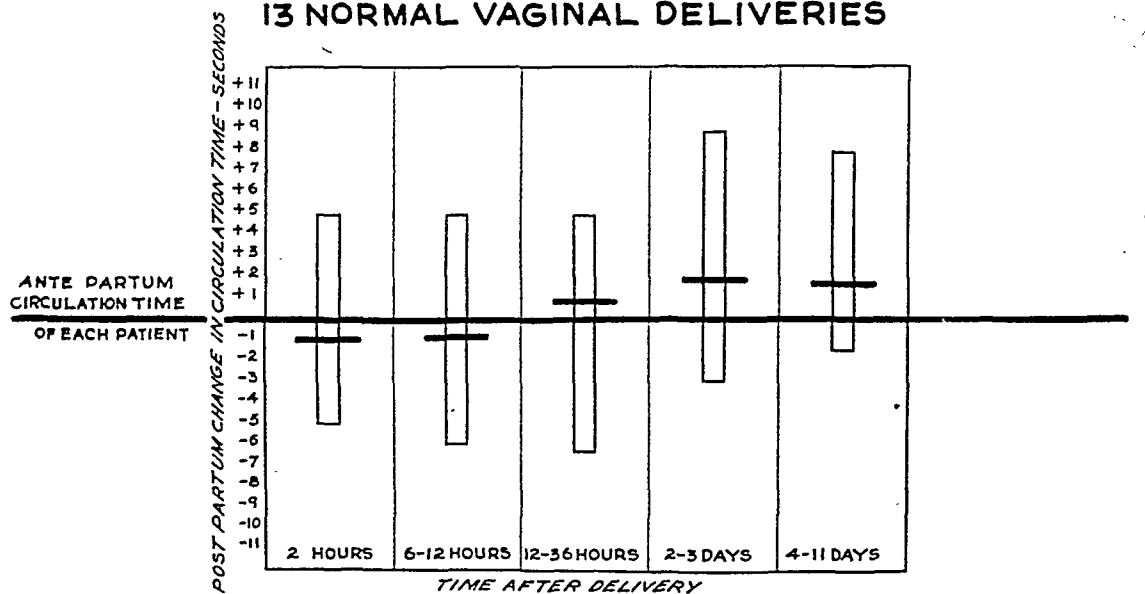
8 (Wh.)	1 (12 hours)	11.5	Oral Intramuscular	4 1	+6.5		+0.3
					30 MINUTES	2 HOURS	
Nonpuerperal females							
1 (Sc.)		10.8	Intramuscular	2†	+11.7 (nausea)	+9.7	+2.2
2 (Gi.)		9.0	Intramuscular	2†	+0.5	-0.5	—
Males							
1 (Bl.)		8.0	Intramuscular	2†	+1.0	—	—
2 (Ar.)		4.8	Oral Intramuscular	1 1	+2.0	+1.0	—
3 (Sa.)		10.3	Oral Intramuscular	1 1	+2.7	+4.2	—
4 (Sm.)		6.0	Intramuscular	2†	+2.0	+4.0	0
5 (Sim.)		5.0	Intramuscular	2†	+2.0	+4.0	+1.0

*When both routes were used, intramuscular injection was at the same time as first oral dose.

†Oral dose was 0.2 mg., repeated every 4 hours. Intramuscular dose was 0.2 mg., given once, 10.4 mg. given in 1 injection.

18.0 seconds, or an average of 12.6 seconds, which is close to the average normal of 13.0 seconds reported by Tarr, Oppenheimer, and Sager.²⁷ Two hours after delivery, the values varied between 7.0 and 20.0, with an average of 11.6 seconds. At the last observation, four to eleven days post partum, the average was 14.4 and the variation between 11.0 and 23.0 seconds. In certain individuals an unusually short circulation time during labor became even shorter two hours after delivery. This is reflected in the average values for the group. There was an

POST PARTUM CHANGE IN CIRCULATION TIME (ARM TO TONGUE) 13 NORMAL VAGINAL DELIVERIES



Columns represent the spreads and heavy cross bars the mean changes. Observed circulation time of each patient is compared with her own ante partum value.

Fig. 2.

overall trend toward acceleration during the first twelve hours, followed by a gradual return to normal rates of circulation during the puerperium, but, as illustrated by Fig. 2, the actual changes which occurred were small and the direction of the changes far from uniform. Following cesarean section and in the patients with cardiac disease, the changes were substantially the same.

6. *Hematocrit.*—The results are shown in Table III. Post-partum hemoconcentration occurred in eight out of the thirteen normal patients who were delivered by the vaginal route and received oxytocic drugs, in two out of three patients with cardiac disease, and in each of two patients delivered by cesarean section. During the puerperium, the hematocrit percentage usually fell and then rose to approach the intra-partum reading. It is to be noted that approximately 180 c.c. of blood were taken from each patient in the course of five to seven determinations of plasma volume.

TABLE III. HEMATOCRIT PER CENT BEFORE AND AFTER DELIVERY

	BEFORE DELIVERY	AFTER DELIVERY				
	STAGE I	2 HOURS	6-12 HOURS	12-36 HOURS	2-3 DAYS	4-11 DAYS
Vaginal deliveries of normal patients						
1 (Ol.)	38.2	41.8	40.3	38.2	36.4	40.4
2 (Sc.)	38.7	40.7	41.2	40.4	41.7	39.3
3 (To.)	32.9	36.0	35.0	35.5	—	32.1
4 (Bu.)	37.5	41.8	39.2	39.3	37.9	38.5
5 (Fr.)	36.6	34.8	34.1	35.0	35.8	35.2
6 (Za.)	41.5	42.8	40.6	42.4	34.8	38.8
7 (St.)	33.0	34.8	34.4	34.6	32.0	32.6
8 (Ny.)	41.8	—	40.4	37.8	38.7	39.1
9 (Cl.)	40.0	39.3	37.3	38.4	33.6	39.0
10 (Wa.)	38.0	36.4	35.9	37.0	37.0	36.6
11 (Du.)	33.1	31.9	33.0	28.3	26.3	28.0
12 (Ba., L.)	44.0	47.2	46.5	46.1	46.6	50.4
13 (Sa.)	43.4	46.7	46.6	42.1	38.5	39.1
Vaginal deliveries of patients with heart disease						
1 (Ch.)	32.3	35.5	—	—	—	26.5
2 (Li.)	38.5	37.6	38.0	34.8	33.9	38.7
3 (Cog.)	36.0	40.6	37.9	34.0	35.6	37.9
	BEFORE OPERATION					
Cesarean sections of normal patients						
1 (Dr.)	44.9	42.3	46.3	45.7	39.0	40.6
2 (Cr.)	40.6	—	43.3	45.2	43.5	43.3

7. *Blood Volume*.—Approximate values for total blood volume, expressed to the nearest 100 c.c., are shown in Table IV. All results are included except those which were discarded because of steep time-concentration curves, hemolysis, or opacity of the serum. In six out of seven cases of normal vaginal delivery, the ante-partum blood volume exceeded the volume predicted for the patient on the basis of her height by 18 to 77 per cent of the predicted volume. If the extremely high two-hour value in Case 10 is disregarded, comparison can be made between the ante-partum value and that found two hours after delivery in four cases of normal vaginal delivery. The volume had decreased 10 per cent or more of the initial value in three cases and increased in one. Six to twelve hours after delivery, the situation was essentially the same. The general tendency toward reduction in blood volume during the first twelve hours after delivery is illustrated further by the two cases of heart disease and one of cesarean section (Table IV), all of whom showed decreases of more than 10 per

cent. Considering all ten cases in which comparison at either two hours or six to twelve hours was possible, blood volume had decreased 10 to 38 per cent in five, increased 13 per cent in one, and was within 10 per cent of the ante-partum value in four cases at the six- to twelve-hour observation. Contrary to expectation, there was no general tendency for the volumes to fall toward normal by the time of the last examination; in fact, extremely high volumes were found four to nine days post partum in several instances. Transient secondary increases in volume occurred between the two-hour and the final observation in several cases.

DISCUSSION

In general, the results are consistent with, but do not prove, the hypothesis that an arteriovenous shunt of important proportions exists in the pelvis at term and that the consequences of its obliteration may contribute to the load imposed on the circulatory system by delivery. This concept is attractive because it provides an orderly pattern into which most of the observations can be arranged, as has been done in interpreting the circulatory changes manifested during pregnancy prior to labor.¹²

The absence of a consistent reduction in heart rate immediately after vaginal delivery does not exclude the possibility of a shunt because in this series of patients, as well as that reported by Pardee and Mendelson,⁵ the heart rate was modified by other factors such as the work of labor, anesthesia, and the effects of oxytocic drugs. The greater tendency to reduction in pulse rate immediately after emptying the uterus by cesarean section, noted also by Burwell and associates,¹³ indicates the possible importance of these factors. It is likely that changes in the blood pressure, such as might be expected to occur after removal of a shunt, are masked in the same way. The slight changes in blood pressure which take place during pregnancy^{13,28,29} are consistent with the shunt hypothesis but may be attributed equally well to increased metabolic rate.

The determinations of vital capacity were included as a basis for future management of patients with heart disease and as an aid to interpreting other findings relative to cardiac failure. In normal patients, no relationship was found between the post-partum rise in venous pressure and changes in vital capacity. A decrease in vital capacity early in the puerperium, followed later by an increase such as occurred in these cases, has also been reported for two larger series.^{30,31} The changes were attributed to mechanical factors affecting ventilation rather than to circulatory embarrassment.

Among several studies of venous pressure in pregnancy and the puerperium,^{12,32-35} observations of the changes taking place in the first twenty-four hours after delivery have been reported only by Dellepiane³³ and Luisi.³⁴ The increased pressure in the antecubital vein observed during this period has been attributed to the effects of lactation.

On the basis of the shunt hypothesis, some elevation of systemic venous pressure after obliteration of the placental circulation might be anticipated without consideration of the action of oxytocic drugs. The situation would be

analogous to that reported by Holman,^{15b} who found transitory cardiac enlargement immediately after occlusion of large arteriovenous fistulae in dogs. Even a normal heart might not be able to accommodate the augmented venous return incident to the severe exercise of labor^{4,36} at a time when overall resistance was increased abruptly following occlusion of a shunt. Transitory cardiac dilatation and high venous pressure might exist until filtration of fluid at high capillary pressures had reduced the volume of circulating blood to fit the vascular compartment.

The experimental results indicate, however, that at least in women with normal hearts, no such transient decompensation follows evacuation of the uterus. The post-partum increase in venous pressure was not immediate and often did not appear until the time of the two-hour examination; and, furthermore, other signs of circulatory embarrassment, such as tachycardia, decreased vital capacity, and increased circulation time usually were not present during periods when venous pressure was maximal.

The results of the studies in which ergotrate was withheld post partum and in which the effects of its administration to puerperal and nonpuerperal patients were observed, indicate that the large and sustained elevations of venous pressure which were seen in all normal patients during the first twenty-four hours after deliveries at which the usual medications were given were caused, at least in part, by the actions of oxytocic drugs. To the reduction in capacity of the vascular tree generally attributed to these agents²⁴ may be added other factors which may have been present to contribute to the high venous pressure, that is, (a) increased return of blood to the heart from exercising muscles,³⁶ (b) autotransfusion of blood expressed from the uterus by the action of oxytocic agents,²⁶ and (c) a possible increase in overall resistance coincident with occlusion of a vascular shunt.

All of these volume factors might be expected to contribute to the precipitation of congestive failure in patients with limited cardiac functional capacity. It has been shown³⁷ that during the uterine contractions of normal labor, arterial inflow to the placenta is greatly diminished and blood contained in the placenta squeezed out. These repeated small autotransfusions might cause transient rises of venous pressure, thus producing filtration of fluid from the capillaries so that total blood volume was gradually diminished during labor. No such gradual preparation for obliteration of the placental circulation is possible in the case of abdominal delivery, which may account for the more prompt rise of venous pressure after abdominal than after pelvic delivery in normal patients (Fig. 1) and also explain, at least in part, the mortality associated with cesarean section in patients with cardiac disease.

In certain cases of congenital heart disease with potential right-to-left intracardiac shunt, alarming situations have been observed to arise at delivery, which were apparently due to increased shunting of the pulmonary circuit.³⁸ When the presence of such lesions is suspected, efforts should be made to avoid sudden increases in the volume of blood presented to the right side of the heart; the slow process of normal labor might be expected to be tolerated better than

abrupt delivery. Furthermore, it would appear that in cases of this type, as well as in others with limited cardiac reserve, the use of ergot derivatives should be reserved for hemorrhagic emergencies.

The changes observed in arm-to-tongue circulation time were not conclusive. However, it is noteworthy that a decided decrease in circulation time occurred on several occasions at times when venous pressure was elevated and maximal hemoconcentration was present. The acceleration which occurs in pregnancy prior to the onset of labor has been attributed by Cohen and Thomson³⁹ to hemodilution and by Burwell¹² to the presence of the placental shunt. The post-partum decrease in the circulation time might reflect a relative increase in the volume of blood passing through cutaneous anastomoses. This interpretation is consistent with the results of plethysmographic studies⁴⁰ in which it was found that blood flow through the muscles of the forearm was unchanged during pregnancy, but that in the hand, where numerous arteriovenous anastomoses exist, blood flow was greatly increased in some patients, not only during pregnancy, but for several weeks after delivery. The part played by metabolic factors in these phenomena has not been demonstrated.

Hemoconcentration had occurred in three-fourths of the cases between the initial determination and that made two hours after delivery. This change and the subsequent hemodilution which appeared with greater uniformity are in agreement with more complete studies, the most recent of which is that of Crawford.⁴¹ On the basis of changes in packed cell volume, plasma protein concentration, and average cell size, and assuming an initial blood volume of 5,000 c.c., he calculated that an average of 590 c.c. of fluid was lost from the blood stream prior to the maximum intrapartum concentration and an average of 745 c.c. was gained to account for the secondary hemodilution. By the end of the second puerperal week, the blood picture had returned to normal.

Although it is well known that blood volume is increased during pregnancy and returns to normal late in the puerperium,^{9,42,43} almost no measurements of blood volume have been made just before and after delivery to confirm this indirect evidence that there is a redistribution of fluid between intravascular and extravascular spaces at this time. Albers,⁴⁴ in an incomplete report, describes an early post-partum decrease in blood volume followed by an increase with hemodilution just prior to the diuresis. Crawford's data indicated that the initial depletion of plasma volume may occur either just before, during, or just after delivery, and this may account for the fact that a significant reduction in plasma volume was shown by comparing the ante partum with the first or second post-partum value in only half of the cases of the present series. The secondary increase in volume was more uniform and often striking. The final determinations of plasma and blood volume may have been made too early to show the return to normal which has been found by other investigators.⁴³

The initial movement of fluid from vascular to extravascular spaces is more likely to be controlled by hemodynamic than humoral factors because it occurs so much earlier than the post-partum diuresis which is usually observed on the third to fifth day.^{45,48} The exact time at which the depletion of plasma volume

occurs after occlusion of large arteriovenous fistulas^{14,17,18} has not been demonstrated; but it is possible that in both this situation and obstetrical delivery the decrease in circulating blood volume results from a sudden increase in overall resistance following obliteration of a shunt. Other factors which may be in operation during labor are (a) osmotic movement of water to exercising muscles, (b) sweating, and (c) filtration through capillary walls during periods of venous congestion, especially late in labor when periods of recovery between uterine contractions are short, and during the first few hours after delivery. For instance, using the unit rate of filtration obtained by Landis and Gibbon⁴⁶ for the human forearm during thirty-minute periods of venous congestion, it may be calculated that a person weighing 50 kilograms might lose 600 c.c. of fluid in the course of forty-three minutes while venous pressure was increased 10 cm. above the resting level.

Secondary hemodilution and increased blood volume, found almost uniformly in this series and by others^{41,44} early in the first week of the puerperium may be partly the result of reabsorption of fluid lost to the tissues during labor but conceivably could be related to the process of removal of extracellular water during the period of negative sodium balance and diuresis.^{45,47,48} More complete and accurate data are required to determine whether the very high blood volumes found on several occasions near the end of the first week of the puerperium were related to mobilization of fluid or were technical artefacts.

The presence of pulmonary edema in a patient with severe cardiac failure after delivery might lead to consideration of therapeutic phlebotomy. Among the arguments for and against this procedure it is important to consider that, in view of the immediate post-partum hemoconcentration, venesection at this time will deprive the patient of a disproportionately large oxygen-carrying capacity. Later in the puerperium, blood loss can be tolerated better.

The rapid rates of disappearance of the dye T-1824 after its injection for determinations of plasma volume, which led to difficulties in interpretation of the results, most often at the ante-partum observation but occasionally after delivery, have not been explained. Among factors which might be considered is the possibility that large pools of blood into which dye diffuses slowly and irregularly may exist in the pelvis, legs, or other reservoirs both before and after delivery. Demonstration of the presence of such pools would be of importance in explaining post-partum circulatory failure in cardiac patients because auto-transfusion of this blood after occlusion of the placental circulation or after administration of oxytocic drugs in the puerperium would affect the volume of venous blood supplied to the heart. More complete studies of the technique of measuring blood volume under these unique conditions are in progress.

SUMMARY AND CONCLUSIONS

1. Repeated determinations of several circulatory functions were made during labor and after delivery in normal patients and in patients with heart disease to determine whether the load imposed on the heart by delivery is pri-

marily the result of (a) the work of labor, (b) more or less sudden obliteration of a vascular shunt in the uterus, or (c) a combination of these and possibly other factors.

2. The changes in heart rate, arterial blood pressure, vital capacity, and circulation time were not sufficiently uniform to point to definite conclusions.

3. Venous pressure increased significantly and often to abnormal levels during the first twenty-four hours after delivery in all patients who received routine medications. Further evidence indicated that this rise of venous pressure could be attributed to the effects of ergotrate. For reasons which have been outlined, it is recommended that ergot derivatives and probably posterior pituitary preparations as well be used with caution in all serious cases of heart disease, especially in the presence of congenital intracardiac shunts.

4. Unusual technical difficulties were encountered in attempting to measure plasma volume with the dye T-1824, both before and after delivery. The results of hematocrit determinations and of those estimations of blood volume which appeared to be technically satisfactory were in agreement with other available evidence indicating that (a) at about the time of delivery a significant volume of fluid leaves the vascular compartment; (b) on the second or subsequent days of the puerperium a volume even greater than this returns to the blood stream; and (c) the final return to normal nonpregnant blood volume probably occurs after this as a result of the post-partum diuresis.

5. Even though the evidence as a whole is inconclusive, the close analogy which has been demonstrated between the changes in blood volume, hematocrit, and venous pressure taking place at delivery and changes known to follow obliteration of large arteriovenous fistulas suggest that the uterus at term contains a shunt of important proportions. The repeated uterine contractions of normal labor, by temporary occlusion of the placental circulation, may prepare the cardiovascular system for permanent occlusion of the shunt. This may explain the clinical impression that vaginal delivery is tolerated as well as or better than cesarean section by patients with serious heart disease.

REFERENCES

1. Hamilton, B. E., and Thomson, K. J.: *The Heart in Pregnancy and the Childbearing Age*, Boston, 1941, Little, Brown & Company, (a) p. 243; (b) p. 53; (c) p. 106.
2. Mackenzie, J.: *Heart Disease and Pregnancy*, London, 1921, Oxford University Press, p. 51.
3. Hoffman, G. D., Jr., and Jeffers, W. A.: Rheumatic Heart Disease Complicating Pregnancy, *Am. J. M. Sc.* 204:157, 1942.
4. Sampson, J. J., Rose, E. M., and Quinn, R.: Estimation of Work of Obstetric Labor and Its Significance in Heart Disease, *Am. J. Obst. & Gynec.* 49:719, 1945.
5. Pardee, H. E. B., and Mendelson, C. L.: Pulse and Respiratory Variations in Normal Women During Labor, *Am. J. Obst. & Gynec.* 41:36, 1941.
6. Mendelson, C. L., and Pardee, H. E. B.: Pulse and Respiratory Rates During Labor as a Guide to the Onset of Cardiac Failure in Women With Rheumatic Heart Disease, *Am. J. Obst. & Gynec.* 44:370, 1942.
7. Mendelson, C. L.: Management of Delivery in Pregnancy Complicated by Serious Rheumatic Heart Disease, *Am. J. Obst. & Gynec.* 48:329, 1944.
8. Gorenberg, H., and McGleary, J.: Rheumatic Heart Disease in Pregnancy, *Am. J. Obst. & Gynec.* 41:44, 1941.

9. Dieckmann, W. J., and Wegner, C. R.: Blood in Normal Pregnancy; Blood and Plasma Volumes, *Arch. Int. Med.* 53:71, 1934.
10. Dieckmann, W. J., and Wegner, C. R.: Studies of Blood in Normal Pregnancy; Hemoglobin, Hematocrit and Erythrocyte Determinations and Total Amount of Variations of Each, *Arch. Int. Med.* 53:188, 1934.
11. Cohen, M. E., and Thomson, K. J.: Studies on Circulation in Pregnancy; Summary of Studies of Physiology of Circulation of Normal Pregnant Women: New Concept of Nature of Circulatory Burden of Pregnancy and Its Application to Management of Clinical Problems of Pregnancy, *J. A. M. A.* 112:1556, 1939.
12. Burwell, C. S.: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to Circulatory Adjustments to Pregnancy, *Am. J. M. Sc.* 195:1, 1938.
13. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Circulation During Pregnancy, *Arch. Int. Med.* 62:979, 1938.
14. Holman, E.: Clinical and Experimental Observations on Arteriovenous Fistulae, *Ann. Surg.* 112:840, 1940.
15. Holman, E.: Arteriovenous Aneurysm: Abnormal Communications Between Arterial and Venous Circulations, New York, 1937, The Macmillan Co., (a) pp. 3-44; (b) p. 29.
16. Reid, M. R., and McGuire, J.: Arteriovenous Aneurysms, *Ann. Surg.* 108:643, 1938.
17. Burwell, C. S., and Kennedy, J. A.: Venous Pressures, Cardiac Output and Blood Volume in Arteriovenous Fistula, *J. Clin. Investigation (Proc.)* 16:671, 1937.
18. Kennedy, J. A., and Burwell, C. S.: Measurements of Circulation in a Patient With Multiple Arteriovenous Connections, *AM. HEART J.* 28:133, 1944.
19. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* 98:475, 1910.
20. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlauftszeit mittels Decholininjektion, *Med. Klin.* 27:986, 1931.
21. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume; Clinical Application of a Method Employing Azo Dye "Evans Blue" and Spectrophotometer, *J. Clin. Investigation* 16:301, 1937.
22. Gibson, J. G., Jr., and Evelyn, K. A.: Clinical Studies of Blood Volume; Adaptation of Method to Photoelectric Microcolorimeter, *J. Clin. Investigation* 17:153, 1938.
23. Noble, R. P., and Gregersen, M. I.: Blood Volume in Clinical Shock. I. Mixing Time and Disappearance Rate of T-1824 in Normal Subjects and in Patients in Shock; Determination of Plasma Volume in Man From Ten Minute Sample, *J. Clin. Investigation* 25:158, 1946.
24. Smith, R. G.: The Present Status of Ergonovine, *J. A. M. A.* 111:2201, 1938.
25. Runge, H.: Ueber den Venendruck in Schwangerschaft, Geburt und Wochenbett, *Arch. f. Gynäk.* 122:142, 1924.
26. Woodbury, R. A., Hamilton, W. F., Abreu, B. E., Torpin, R., and Fried, P. H.: Effects of Posterior Pituitary Extract, Oxytocin (Pitocin) and Ergonovine Hydracrylate (Ergotrate) on Uterine, Arterial, Venous and Maternal Effective Placental Arterial Pressures in Pregnant Humans, *J. Pharmacol. & Exper. Therap.* 80:256, 1944.
27. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: Circulation Time in Various Clinical Conditions Determined by Use of Sodium Dehydrocholate, *AM. HEART J.* 8:766, 1933.
28. Henry, J. S.: Effect of Pregnancy Upon Blood-pressure, *J. Obst. & Gynaec. Brit. Emp.* 43:908, 1936.
29. Landt, H., and Benjamin, J. E.: Cardiodynamic and Electrocardiographic Changes in Normal Pregnancy, *AM. HEART J.* 12:592, 1936.
30. Thomson, K. J., and Cohen, M. E.: Studies on Circulation in Pregnancy; Vital Capacity Observations in Normal Pregnant Women, *Surg., Gynec. & Obst.* 66:591, 1938.
31. Alward, H. C.: Observations on Vital Capacity During Last Month of Pregnancy and Puerperium, *Am. J. Obst. & Gynec.* 20:373, 1930.
32. McLennan, C. E.: Antecubital and Femoral Venous Pressure in Normal and Toxemic Pregnancy, *Am. J. Obst. & Gynec.* 45:568, 1943.
33. Dellepiane, G.: La pressione venosa studiata con metodo diretto nel campo ostetrico, *Riv. ital. di ginec.* 6:145, 1927.
34. Luisi, M.: Sul contegno e sul significato della pressione venosa periferica nelle tossicosi gravidiche, *Riv. ital. di ginec.* 21:1, 1938.

35. Thomson, K. J., Reid, D. R., and Cohen, M. E.: Studies on Circulation in Pregnancy; Venous Pressure Observations in Normal Pregnant Women, in Pregnant Women With Compensated and Decompensated Heart Disease and in Pregnancy Toxemias, *Am. J. M. Sc.* 198:665, 1939.
36. Schneider, E. C., and Collins, R.: Venous Pressure Responses to Exercise, *Am. J. Physiol.* 121:574, 1938.
37. Woodbury, R. A., Hamilton, W. F., and Torpin, R.: Relationship Between Abdominal, Uterine and Arterial Pressures During Labor, *Am. J. Physiol.* 121:640, 1938.
38. Carr, F. B., and Hamilton, B. E.: 500 Women With Serious Heart Diseases Followed Through Pregnancy and Delivery, *Am. J. Obst. & Gynec.* 26:824, 1933.
39. Cohen, M. E., and Thomson, K. J.: Studies on Circulation in Pregnancy; Velocity of Blood Flow and Related Aspects of Circulation in Normal Pregnant Women, *J. Clin. Investigation* 15:607, 1936.
40. Abramson, D. I., Flachs, K., and Fierst, S. M.: Peripheral Blood Flow During Gestation, *Am. J. Obst. & Gynec.* 45:666, 1945.
41. Crawford, M. D.: Changes in Blood Concentration in Normal and Toxaemic Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* 47:63, 1940.
42. Miller, J. R., Keith, N. M., and Rowntree, L. G.: Plasma and Blood Volume in Prgenancy, *J. A. M. A.* 65:779, 1915.
43. Thomson, K. J., McGregor, M., Hirsheimer, A., Gibson, J. G., II, and Evans, W. A., Jr.: Studies in Circulation in Pregnancy; Blood Volume Changes in Normal Pregnant Women, *Am. J. Obst. & Gynec.* 36:48, 1938.
44. Albers, H.: Blutmengen- und Wasserbewegungen in der Schwangerschaft und unter der Geburt, *Zentralbl. f. Gynäk.* 63:1377, 1939.
45. Taylor, H. C., Warner, R. C., and Welsh, C. A.: Relationship of Estrogens and Other Placental Hormones to Sodium and Potassium Balance at End of Pregnancy and in Puerperium, *Am. J. Obst. & Gynec.* 38:748, 1939.
46. Landis, E. M., and Gibbon, J. H., Jr.: The Effects of Temperature and of Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, *J. Clin. Investigation* 12:105, 1933.
47. Chesley, L. C.: Weight Changes and Water Balance in Normal and Toxemic Pregnancy, *Am. J. Obst. & Gynec.* 48:565, 1944.
48. Taylor, H. C., Jr., Warner, R. C., and Welsh, C. A.: Relationship of Estrogens and Progesterone to Edema of Normal and Toxemic Pregnancy, *Am. J. Obst. & Gynec.* 45:547, 1943.

VOLUNTARY ACCELERATION OF HEART IN A SUBJECT SHOWING THE WOLFF-PARKINSON-WHITE SYNDROME

CLINICAL, PHYSIOLOGIC, AND PHARMACOLOGIC STUDIES

HAROLD FEIL, M.D., HAROLD D. GREEN, M.D.,
AND DONALD EIBER, M.D.*
CLEVELAND, OHIO

VOLUNTARY acceleration of the heart has been reported and studied in at least twenty cases.¹⁻¹¹ Most of the subjects have been students in physiology, medical students, or physicians. It is not unlikely that the incidence of voluntary acceleration of the heart may be much more frequent than the few cases in the literature suggest. We are reporting the twenty-first case. The subject (D. E. E., age 23), while an undergraduate student in medicine, discovered his ability to voluntarily speed his heart rate. We present this case report because of the unique association of the Wolff-Parkinson-White syndrome. Our work includes physiologic and pharmacologic studies made in an effort to elucidate the mechanism of the control of his heart rate and the accompanying symptoms.

CASE REPORT

Clinical History.—Two years before the present observations were undertaken, D. E. E. tried voluntarily to dilate his pupils by using the principle of the fear response. He decided to recall an emotion of fear—a frightening nightmare experienced four years previously when he was lost in the Canadian wilds. He wrote out his experiences and re-enacted them in his imagination. This experience was practised daily for four weeks, with intense concentration on the climax of the story. He observed the dilation of his pupils in a mirror and noted the accompanying sensations, which included tachycardia. After repeated experiences he was able to dissociate the effort to dilate his pupils and to concentrate on the will to accelerate his heart and found that he was successful. After an interval of a year he found again that he was able to control his heart rate at will. Upon concentration and the sudden acceleration of the heart he felt as if subjected to an explosion, and had paresthesia of the hands and feet, tinnitus, and palpitation. On willing his heart to slow he felt relaxed and had a sensation of relief and of fatigue. He frequently felt dissociated from his environment. Euphoria and a sensation of numbness often followed. The only other pertinent fact in the history was the occurrence of attacks of paroxysmal tachycardia five or six times a year, lasting two or three hours. These attacks started and stopped suddenly and were unrelated to any effort at voluntary acceleration. One of us (H. F.) observed the subject in one of these attacks. The rate was 180 per minute and the rhythm was regular. The attack had lasted thirty minutes before observation and was readily stopped by right carotid sinus pressure. No electrocardiogram was taken at this time.

Read at the Second Inter-American Congress of Cardiology, Mexico, D. F., Oct. 5-12, 1946.

Received for publication Jan. 7, 1947.

*From the Departments of Medicine and of Physiology, Western Reserve University School of Medicine, and from Lakeside Hospital.

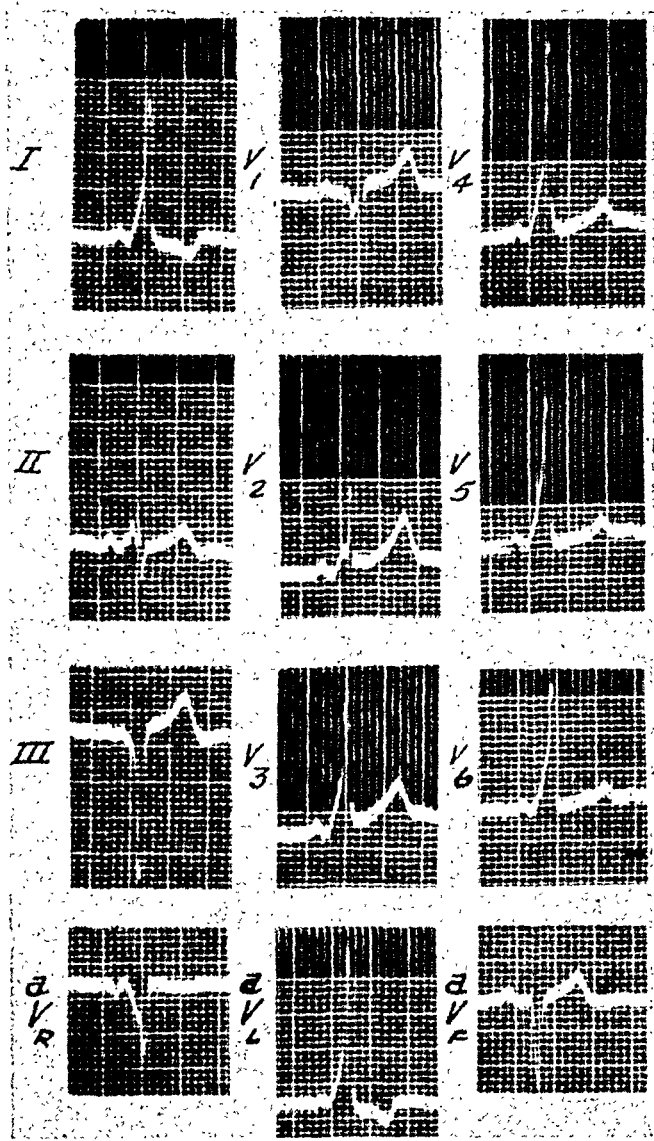


Fig. 1.—Electrocardiogram showing the characteristics of the Wolff-Parkinson-White syndrome.

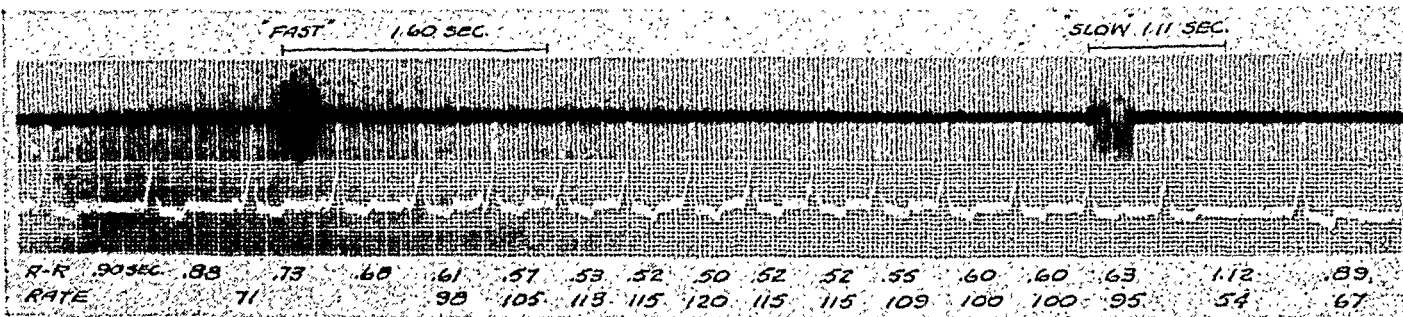


Fig. 2.—Electrocardiogram demonstrating voluntary speeding and slowing of the heart rate.

Examination.—Examination did not reveal any evidence of abnormality, except that the electrocardiogram was typical of the Wolff-Parkinson-White syndrome (short P-R interval and prolonged QRS complex). The chest leads placed this case in the "B" classification (Fig. 1) as described by Rosenbaum and associates.¹² The P-R interval is 0.10 second and the QRS interval is 0.13 second. The limb leads have the appearance of left bundle branch block. Lead V_1 shows that the intrinsicoid deflection begins 0.06 second after the onset of QRS; V_3 and V_6 show this intrinsicoid deflection beginning 0.09 second after the onset of QRS. There appears to be a delay over both ventricles but the delay is greater over the left ventricle.

STUDIES

Typical Experiment.—The subject reclined on a comfortable bed and was attached to an electrocardiograph. The stethograph was used to register simultaneously with the electrocardiogram the orders "fast," "slow," and "relax." Fig. 2 is a typical experiment with control, "fast," and "slow" periods. The normally pronounced sinus arrhythmia almost disappears during cardiac acceleration. The measurement of cycle lengths and corresponding heart rates is given below the record. The orders "fast" and "slow" are easily seen in the sound track above the electrocardiogram. The resting control heart rate was 71 per minute. Exactly 1.60 seconds after the order "fast" the rate rose to 98, the fifth cycle rising to a rate of 120. The rate fell slightly (to 95) at the time the order "slow" was given. Just 1.12 seconds after the order "slow" the rate fell to 54 per minute. A pneumogram taken simultaneously showed that the respiratory rate increased up to 30 per minute and the respirations were very slight in depth. Table I is a summary of four of the experiments which serve as some of the controls.

Effect of Posture.—Vagus tone increases with the normal subject in the reclining position and decreases when the upright position is assumed.¹³ Voluntary acceleration was performed in the two positions as shown in Table II. The standing rate increased over the dorsal rate. The average rate rose from 74 to 93 in the control observation. Acceleration occurred in the dorsal position in 1.56 seconds (average of four experiments). Acceleration in the standing position took place in 1.27 seconds, the rate increasing less because the control standing rate was faster. The rate after the order "fast" reached 121 faster than the rate in the reclining position. In summary, the lessening of vagus tone in the upright position did not have any significant influence on the acceleration mechanism.

Carotid Sinus Pressure Observations.—The effect of right and left carotid sinus pressure was studied in relation to the acceleration and deceleration of the heart. All the experiments were made with the subject in the recumbent position. Table III is a summary of the data. No slowing followed carotid sinus pressure. The acceleration was of the same degree as in the control experiments of Table I. The latent periods of acceleration and of deceleration were unchanged. Therefore, the influence of the vagus under the augmentation of carotid sinus pressure, both right and left, appeared to have no influence on the speeding up and slowing of the heart.

TABLE III. EFFECTS OF CAROTID SINUS PRESSURE ON THE ABILITY TO VOLUNTARILY CONTROL HEART RATE

	HEART RATE CONTROL	RATE AFTER CAROTID SINUS PRESSURE	NET CHANGE	CAROTID SINUS PLUS "ACCELE- RATION"	PER CENT ACCELERATION	LATENT PERIOD OF ACCELERATION (SEC.)	HEART RATE "SLOW"	LATENT PERIOD OF "SLOW" (SEC.)
Right	75	81	+ 6	111	37	1.73	71	1.00
Right	63	69	+ 6	126	27	1.45	63	1.98
Left	57	56	- 1	88	48	1.20	53	1.67
Left	56	64	+ 8	83	44	1.41	53	1.53
Left	56	56	0	92	54	1.18	52	1.49
				86				

Respiration.—The electrocardiogram was taken simultaneously with the pneumograph attached to the chest and to the abdomen. Control respiration was 18 per minute and the heart rate was 67 per minute. Forced acceleration of respiration to 28 per minute increased the heart rate to 73 per minute. When the respiratory rate fell to 13, the heart rate was 98. In another experiment the respiratory rate was increased purposefully from 15 to 30 per minute. During the period of tachypnea the order "fast" was given and the heart rate increased from 65 to 104 per minute, and fell to 57 on the order "slow."

Changes in Intrathoracic Pressure.—In normal persons vagus tone varies with the phases of respiration, the heart rate increasing toward the end of inspiration (decrease in intrathoracic pressure) and slowing at the end of expiration (increase in intrathoracic pressure). With these facts in mind voluntary acceleration was performed under the conditions of Valsalva's experiment (forced expiration with the glottis closed) and Müller's experiment (forced inspiration with the glottis closed). (Table IV.)

TABLE IV. EFFECTS OF THE VALSALVA AND MÜLLER EXPERIMENTS UPON VOLUNTARY ACCELERATION

	HEART RATE			LATENT PERIOD	
	CONTROL	FAST	SLOW	CONTROL-TO-FAST (SEC.)	CONTROL-TO-SLOW (SEC.)
Valsalva's experiment (expiration)	69	105 + 36	95	2.92	1.97
Müller's experiment (inspiration)	75	112 + 37	76	2.71	1.55

Effect of Deep Inspiration and Breath-holding.—The subject inspired deeply and held his breath for ten seconds, at which time the order "fast" was given. The heart rate rose from 78 to 95 in 1.25 seconds. The rate rose later to 134. In 1.50 seconds after the order "slow," the rate fell to 77.

Duodenal Peristalsis and Voluntary Acceleration.—A small balloon inflated to a pressure of 5 mm. Hg was inserted in the duodenum (by fluoroscopic control) and the peristalsis studied. During the control period duodenal peristaltic waves occurred at a rate of 14 to 21 per minute. With voluntary acceleration the peristaltic waves persisted at the same rate.

Eye Changes (Observations by Dr. L. V. Johnson).—On inspection during the control period hippus was observed. With the order "fast" the pupil dilated slightly, the hippus persisting. There was slight pulsation of the retinal veins during "acceleration." Following the order "slow" the veins collapsed. Dilation of the pupils persisted for a few minutes following acceleration.

Blood Pressure.—Observations of the blood pressure were made in the control experiments and in many of the others. The average control blood pressure was 128/70. With acceleration the pressure was 180 systolic and 94 diastolic. With deceleration the pressures fell to the control level.

Gastrointestinal Roentgenographic Studies.—The stomach and small intestines were observed after the ingestion of barium. No changes in peristalsis were noted during the period of acceleration. The barium passed through the small intestines at a normal rate. The examination was done by Dr. Carroll C. Dundon, to whom we are indebted.

Effort to Slow the Heart Without Previous Acceleration.—The subject attempted to slow his heart rate from the resting control rate. On several occasions when this was tried no change in heart rate occurred.

Electroencephalogram (We are indebted to Dr. C. T. Randt for these observations and interpretations).—A four channel amplifier and Grass ink-writing oscillograph were used to record brain and heart potentials. An electroencephalogram with both monopolar and bipolar tracings from occipital, postcentral, precentral, and frontal areas, with the reference electrode for monopolar recording attached to both ear lobes, was taken. There was no abnormality from either hemisphere, from homologous areas on both sides, or after two minutes and thirty seconds of hyperventilation. A dominant ten per second alpha rhythm was most prominent in occipital leads bilaterally.

Electrode placements on both upper arms with a three per cent gain, as opposed to twenty-five per cent gain for the brain potentials, were used to simultaneously record the electrocardiogram.

The electroencephalogram taken with the subject's eyes closed showed blocking of the alpha rhythm concomitant with the onset of voluntary acceleration of the heart rate. The alpha activity (10 per second) was suppressed, showing a decrease in amplitude and less frequent occurrence. Toward the end of each fifteen-second period of acceleration, the alpha rhythm again became more prominent. Similar blocking was observed on subsequent voluntary slowing of the heart rate with reappearance of alpha rhythm before the signal to relax was given.

Identical depression of the regular 10 per second waves was produced in the record by opening the eyes in a lighted room, by turning a flashlight beam on the subject's eyes, and by having him solve an arithmetical problem with his eyes closed.

In 1930, Berger¹⁸ noted that any type of visual, auditory, or tactile stimulation which serves to attract the patient's attention tends to decrease the amplitude and occurrence of the alpha rhythm. The depression of the occipital alpha rhythm is probably a centrally determined response since it can be induced by hypnosis and attention.

The characteristic blocking response to attention was produced with voluntary acceleration of the heart rate.

Persistence of Acceleration.—An experiment to determine the ability of the subject to maintain sustained acceleration was performed. The control rate was 76; 1.12 seconds after the order "fast" was given the rate rose to 109 and in five cycles rose to 146, an increase of 70 beats per minute. He was able to maintain acceleration for one minute and fifty-five seconds, the rate falling to 84 at the end of the experiment. At this time the subject was exhausted and the experiment was stopped.

Heart Sounds.—The heart sounds were recorded simultaneously with the electrocardiogram. The first vibrations of the first heart sound occurred 0.08 second after the onset of QRS and at the apex of R (Fig. 3).

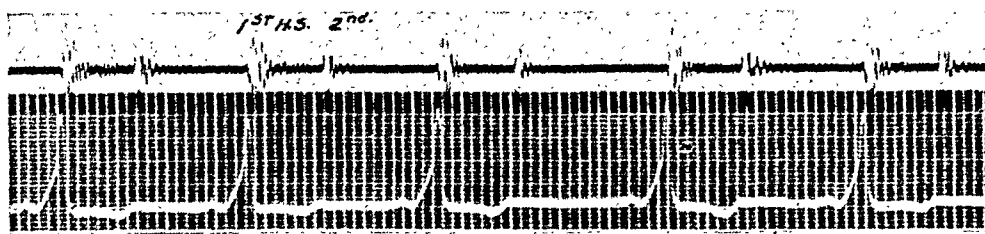


Fig. 3.—Simultaneous phonocardiogram and electrocardiogram. The first sound begins 0.08 second after the onset of the QRS complex.

Subclavian Pulse.—Optical records of the subclavian pulse were taken. During the period of acceleration the height of the waves was reduced, reflecting the reduced output per beat. There was no significant change in contour.

Peripheral Blood Flow.—Plethysmographic studies of the volume in the hands by Dr. A. S. Harris revealed a diminution during the period of acceleration. Control experiments with arithmetic problems failed to show a similar diminution. These studies suggest that sympathetic control is a prime factor in the speeding up of the heart. Similar results were reported in one of the earlier cases.⁷

Effect of Violent Exercise.—The subject climbed 100 steps rapidly and the respiratory rate increased to 35 per minute. The heart rate increased to 147 per minute. On the order "fast" the rate rose to 148 and on the order "slow" fell to 101 beats per minute. No abrupt change in rate occurred.

Adrenalin.—Adrenalin was injected subcutaneously (0.5 c.c., 1:1000 solution) after control studies. The data are seen in Table V. The usual subjective and objective symptoms, including a feeling of tension, palpitation, and body tremor, occurred. The heart rate rose to 112 per minute and the blood pressure to 150/80. Acceleration occurred following the order "fast" in about the usual time and to the same degree. The fastest rate was higher than in the control experiments. The slowing occurred in the usual interval although the rate was higher than in the control group.

Adrenalin augments the accelerator effect but does not prevent the ability of the subject to slow his heart quickly. It was decided to study the persistence

TABLE V. EFFECT OF ADRENALIN UPON ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE	LAST OF FAST RATE	DURATION OF FAST RATE (SEC.)
Control	63	97	2.02	50	1.27	116/70		
Control	52	95	1.64	46	.91			
Control	56	87	2.24	58	2.34	150/80	72	74
4 minutes after adrenalin								
5½ minutes after adrenalin	63	90-123	2.16	87	2.13		119	103
16 minutes after adrenalin	73	107-120	1.52	84	1.50	150/80		
21 minutes after adrenalin	112	136	2.24	83	2.12	150/80		

of the tachycardia under control conditions and after adrenalin. The subject was requested to accelerate his heart and continue the fast rate as long as possible. He was able to maintain the increased rate for one minute and fourteen seconds. He was then ordered to slow his heart because of fatigue. Five and one-half minutes after 0.5 c.c. of adrenalin, he again was requested to speed his heart. This acceleration lasted one minute and thirty-eight seconds before fatigue caused us to order the subject to slow his heart. Numerous premature beats of ventricular origin caused trouble in measuring the latent period in some records. The data of the persistence experiment are summarized in Table VI.

Adrenalin augmented the subject's ability to speed the heart. He was able to continue the accelerated rate for a longer period, but he was still able to slow his heart quickly.

TABLE VI. RESULTS OF ATTEMPTS TO SUSTAIN ACCELERATION BEFORE AND AFTER ADRENALIN

	CON- TROL RATE	FAST	CONTROL- TO-FAST	PERSISTENCE TIME	FASTEST RATE	FAST-TO- SLOW	RATE AT TIME OF SLOWING	SLOW
Control experiment	56	87	2.24 sec.	1 min., 14 sec.	98	2.34 sec.	68	54
After adrenalin	63	90	*	1 min., 38 sec.	123	1.85 sec.	110	87

*Cannot be measured because of premature beats.

Ergotamine Tartrate.—Ergotamine tartrate does not affect the sympathetic control of the heart,¹⁴ but does slow the heart even after atropine. It also increases the excitability of the vagus to electric stimulation and to acetylcholine.¹⁵ It slows sinus rhythm through direct action on the sinus node.¹⁶ Ergotamine tartrate (0.5 mg.) was injected subcutaneously after a preliminary rest period and after control records were taken. A second dose of 0.5 mg. was given twenty-five minutes after the first injection. The results are summarized in Table VII.

In spite of the slowing effect on the control rates (74 to 47) the subject was still able to effect acceleration and to slow his heart in approximately the same intervals of time as before the injection of ergotamine. This suggests that the mechanism of acceleration was predominantly via sympathetic action.

Acetyl-beta-methylcholine.—The subject gave a history of asthma, so that two doses of 7.5 mg. were given (the second dose being given seven minutes after the first). Two minutes after the second dose the subject had flushing of the face, sweating, fullness of the head, salivation, and some dyspnea. Further use of choline was discontinued. The heart rate rose from 57 to 109 and the blood pressure from 130/66 to 148/50. The data of this experiment are given in Table VIII. No conclusions may be drawn from this experiment. The small dose was probably the cause of the increase in heart rate because of the action of the drug on the pacemaker.

TABLE VII. EFFECTS OF ERGOTAMINE TARTRATE ON THE ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE
Control	74	111	1.72	58	.96	126 systolic
13 min. after 0.5 mg. ergotamine tartrate	60	100	1.70	59	1.52	126 systolic
15 min. after	50	92	1.57	51	1.84	
31 min. (0.5 mg., 2nd dose)	49	83	1.69	48	1.56	
43 min.	47	80	1.53	46	1.79	
45 min.	48	46		43		
		Rt. C.S.P.		C.S.P. off		
47 min.	47	44		45		
		Rt. C.S.P.		C.S.P. off		
51 min.	46	43		50		
		Lt. C.S.P.		C.S.P. off		
53 min.	44	49 F79	1.43	43 47	1.17	
		Lt. C.S.P.		C.S.P. off		
55 min.	48	53 78	2.02	45 51	1.45	
58 min.	44	46 78	1.64	44 42	.88	
		Rt. C.S.P.				
61 min.	46	48 79	.96	45 49	.72	

TABLE VIII. INFLUENCE OF ACETYL-BETA-METHYLCHOLINE ON ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE
Control	57	96	2.10	83	1.20	130/66
5 mg. BMAC	109	159	2.80	112	1.98	148/50

Atropine.—Atropine has been used by a number of investigators to determine the effect of inhibition of the parasympathetic nervous system. Favill and White⁶ showed that their subject could accelerate his heart even after atropine. A study of the effect of atropine was made in our case. Two mg. of atropine sulphate were injected hypodermically. The maximum effect occurred twenty-five minutes after the injection when his heart rate was 139 beats per minute. On the order "fast" the rate increased to 146, and within 10.2 seconds to 165. On the order "slow" the rate fell to 155, and then to 139. Later, two more efforts to accelerate the heart (with control rates of 135) were not followed by acceleration. Thus, it is seen that vagal inhibition may have played a part in the voluntary acceleration and slowing.

Amyl Nitrite.—Amyl nitrite was inhaled by the subject to determine the effect of cardiac acceleration and lowered diastolic blood pressure. Acceleration was attempted while inhaling amyl nitrite. The data are summarized in Table IX.

TABLE IX. INFLUENCE OF AMYL NITRITE UPON VOLUNTARY CONTROL OF HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	RELAX*
Control	69	125	1.34	63	1.21	
Amyl nitrite	76	129				
Amyl nitrite	83	125	1.28	170		136

*Subject requested to relax.

Inhalation of amyl nitrite resulted in moderate tachycardia in the control observation. When voluntary acceleration was attempted the heart rate rose from 83 to 125 and later to 157. When told to "slow" the heart, the rate increased from 157 to 170, gradually. When told to "relax" the rate gradually fell to 136. Thus, voluntary acceleration probably was moderately effective immediately; but the rate rose to 157 subsequently. When told to "slow," the heart rate was not under control of the will because of the reflex from the carotid sinus and also because of reflex depression of the vagus center.¹⁷ Amyl nitrite did not abolish the abnormal ventricular complexes.

Digitalis.—The effect of digitalis was studied because of its profound action on the vagus nerve and on the heart muscle. The subject was given 1.8 Gm. of digitalis powder in 24 hours and studied. Digitalization did not abolish the anomalous excitation of the ventricles. The results of this experiment are given in Table X.

TABLE X. DIGITALIS AND VOLUNTARY ACCELERATION

CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)
52	79	1.74	45	1.54

The increase in heart rate after "fast" was 27 beats, or 52 per cent; proportionally as great as in the control experiments. The responses to "slow" were equally effective and fast. Vagal influence does not interfere with the acceleration mechanism, with the subject digitalized.

Quinidine.—Quinidine has been reported as effective in abolishing the anomalous conduction.¹² The administration of 2 Gm. of quinidine sulphate did restore normal conduction as illustrated in Fig. 4.

Again augmentation of the vagus effect did not prevent acceleration of the heart to the usual degree. (Table XI.)

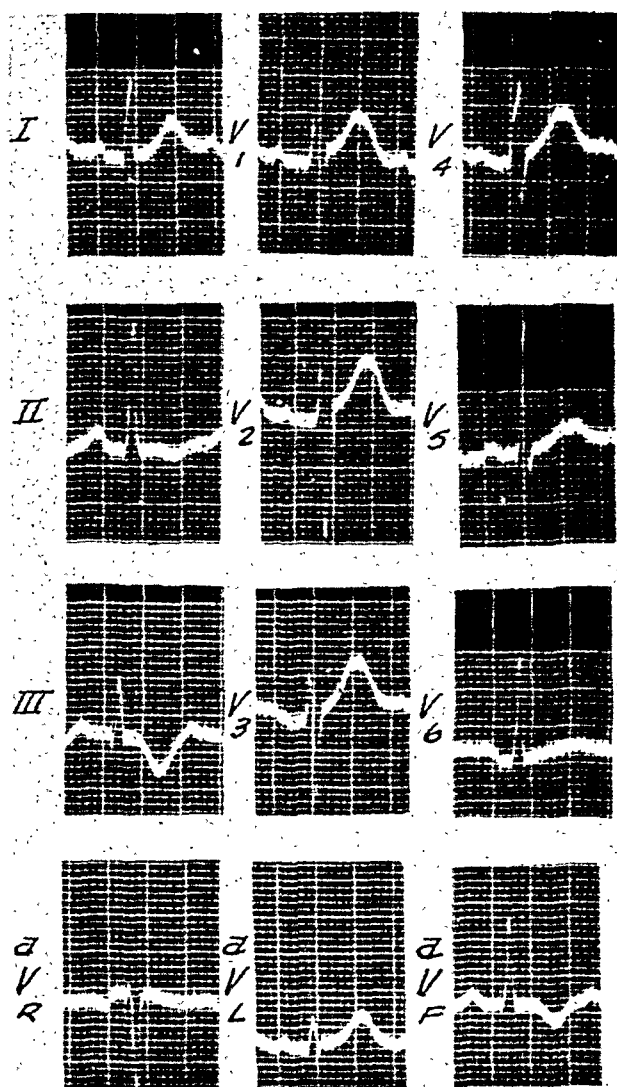


Fig. 4.—Restoration of normal conduction by quinidine.

TABLE XI. QUINIDINE AND VOLUNTARY ACCELERATION

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	ECG
Control	55	85	1.73	46	1.57	W. W. P. S.
2 Gm. quinidine	105	120	2.36	101	2.44	N. M.
24 hrs. later	67	91	1.36	55	1.22	W. W. P. S.

DISCUSSION

The evidence suggests that the voluntary acceleration is due preponderantly to sympathetic action. Acceleration occurred after adrenalin, as well as after atropine, but the increase was greater after adrenalin. The acceleration was definite twenty-five minutes after atropine, but later the control rate of 135 was not increased by the order "fast." This may have been due to fatigue, as the subject had noted previously that his facility to voluntary acceleration decreased with repeated trials. The voluntary slowing after acceleration was not altered by atropine (in the early experiments) or by adrenalin. The inhalation of amyl nitrite did not prevent voluntary acceleration, but the progressive increase in heart rate on the order "slow" may have been the result of the amyl nitrite. The fact that drugs increasing vagus effect (ergotamine, digitalis, and quinidine) do not alter the ability of the subject to speed up and slow his heart suggests that vagus action may be in part involved. This is in keeping with the idea that cardiac function results from the balance between the activities of the sympathetic and the parasympathetic divisions of the autonomic system. The evidence of the electroencephalogram shows that the subject did have cerebral activity preceding the acceleration, as in any thought process.

CONCLUSIONS

1. This twenty-first reported case of voluntary acceleration and deceleration of the heart is unique in its association with anomalous ventricular excitation (Wolff-Parkinson-White syndrome).

2. Adrenalin and atropine given in physiologic doses do not prevent the ability of the subject to control his heart action. Adrenalin appears to have an augmenting effect on acceleration.

3. Drugs increasing vagus tone (digitalis, quinidine, and ergotamine tartrate) do not prevent the acceleration and deceleration.

4. No physical means of acceleration (changes in respiration or muscular activity) were demonstrated.

5. The electroencephalogram demonstrated that psychic activity preceded the acceleration.

6. The diminution in the peripheral blood flow and the dilation of the pupils further substantiate the importance of the impulses via the sympathetic system.

7. The ability of the subject to influence his heart rate was chiefly through sympathetic control, but inhibition and augmentation of vagus influence also played a part.

REFERENCES

1. Tüke, D. H.: *Illustrations of the Influence of the Mind Upon the Body in Health and Disease Designed to Elucidate the Action of the Imagination*, ed. 2, Philadelphia, 1884, Henry C. Lea's Son & Co., p. 372.
2. Tarchanoff, J. R.: Ueber die willkürliche Acceleration der Herzschläge beim Menschen, *Pflüger's Arch. f. d. ges. Physiol.* 35:109, 1885.
3. Pease, E. A.: *Voluntary Control of the Heart*, Boston, M. & S. J. 120:525, 1889.

4. Van de Velde, Th. H.: Ueber willkürliche Vermehrung der Pulsfrequenz beim Menschen, Arch. f. d. ges. Physiol. 66:232, 1897.
5. Koehler, Max: Ueber die willkürliche Beschleunigung des Herzschlages beim Menschen, Pflüger's Arch. f. d. ges. Physiol. 158:579, 1914.
6. Favill, J., and White, P. D.: Voluntary Acceleration of the Rate of the Heart Beat, Heart 6:175, 1917.
7. West, H. F., and Savage, W. E.: Voluntary Acceleration of Heart Beat, Arch. Int. Med. 22:290, 1918.
8. Carter, E. P., and Wedd, A. M.: Report of a Case of Paroxysmal Tachycardia Characterized by Unusual Control of the Fast Rhythm, Arch. Int. Med. 22:571, 1918.
9. Taylor, N. B., and Cameron, H. G.: Voluntary Acceleration of the Heart, Am. J. Physiol. 61:385, 1922.
10. Carpenter, T. M., Hoskins, R. G., and Hitchcock, F. A.: Voluntary Induced Increases in Rates of Certain "Involuntary" Physiological Processes of Human Subject, Am. J. Physiol. 110:320, 1934.
11. Ogden, E., and Shock, N. W.: Voluntary Hypercirculation, Am. J. M. Sc. 198:329, 1939.
12. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), AM. HEART J. 29:281, 1945.
13. Moss, A.: Application de la balance á l'étude de la circulation du sang chez l'homme, Arch. ital. de biol. 5:130, 1884.
14. Otto, H. L.: Upon Action of Ergotoxin, in Mammalian Heart, J. Pharmacol. & Exper. Therap. 33:285, 1928.
15. Sollmann, T.: A Manual of Pharmacology, Philadelphia, 1943, W. B. Saunder, p. 516.
16. Andrus, E. C., and Martin, L. E.: Action of Sympathetic Upon Excitatory Process in Mammalian Heart, J. Exper. Med. 45:1017, 1927.
17. Rothlin, E.: Ergotamine, Arch. Internat. de pharmacodyn. et de therap. 27:459, 1923.
18. Berger, H.: Ueber das Elektrenkephalogramm des Menschen, J. f. Psychol. u. Neurol. 40:160, 1930.

SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

LEO LOEWE, M.D., AND HAROLD B. EIBER, M.D.
BROOKLYN, N. Y.

OF A current series of 166 patients with subacute bacterial endocarditis, we have encountered eleven (7 per cent) with consistently sterile blood cultures despite recourse to anaerobic methods, enriched mediums, arterial punctures, and cultures taken after the administration of epinephrine.* The diagnosis in two of our patients was confirmed by necropsy findings. In the remainder, the recognition of the presence of the syndrome was dependent upon the classical manifestations of protracted fever, valvulitis, embolic phenomena, and usually a splenomegaly. Needless to say, the other possible etiological factors in a prolonged pyrexia were excluded by extensive laboratory investigations.

This communication has for its purpose a summation of eleven histories, a report of the responses to therapy, and the suggestion that the response to treatment with anti-infective agents be employed in the future as a therapeutic test.

CASE REPORTS

CASE 1.—Subacute bacterial endocarditis, eighteen months: primary rheumatic cardio-valvular lesion of mitral and tricuspid valves; no response to fourteen days of penicillin-heparin therapy.¹⁻⁷ Necropsy findings: thromboulcerative mitral endocarditis, healed rheumatic endocarditis of mitral and tricuspid valves, multiple infarcts, avitaminosis, and cachexia; cultures of valves sterile, colonies of organisms in histopathologic section of valves.

C. M. T., a 48-year-old white man, was known to have had a heart murmur since early childhood, with no actual diagnosis of rheumatic fever or scarlatina. He entered the Jewish Hospital of Brooklyn on July 6, 1944, complaining of chills, fever, weakness, loss of weight, nausea, and petechiasis. Eighteen months prior to the onset of this illness he had "flu" which lasted for about three days. The fingers became clubbed and he developed splenomegaly. During the past twelve months he lost approximately forty pounds in weight.

On examination he was found to be an emaciated, chronically ill man who was very pale, with a suggestive cafe-au-lait complexion. There was a presystolic rumble at the apex and a systolic murmur heard over the entire precordial area. The blood pressure was 90/46. The spleen was palpable 5 cm. below the costal margins. The liver was enlarged to 7 cm. below the costal margins. There was clubbing of the fingers.

The clinical impression was subacute bacterial endocarditis engrafted on a rheumatic heart lesion. X-ray examination revealed considerable enlargement of the heart with aortic and mitral

Aided by a grant from the John L. Smith Fund for Medical Research, Jewish Hospital of Brooklyn. From the Department of Medicine and the Department of Laboratories, Jewish Hospital of Brooklyn.

Received for publication Nov. 25, 1946.

*Epinephrine technique for obtaining positive blood cultures was originally suggested by Dr. Myron Prinzmetal and Dr. B. S. Oppenheimer.

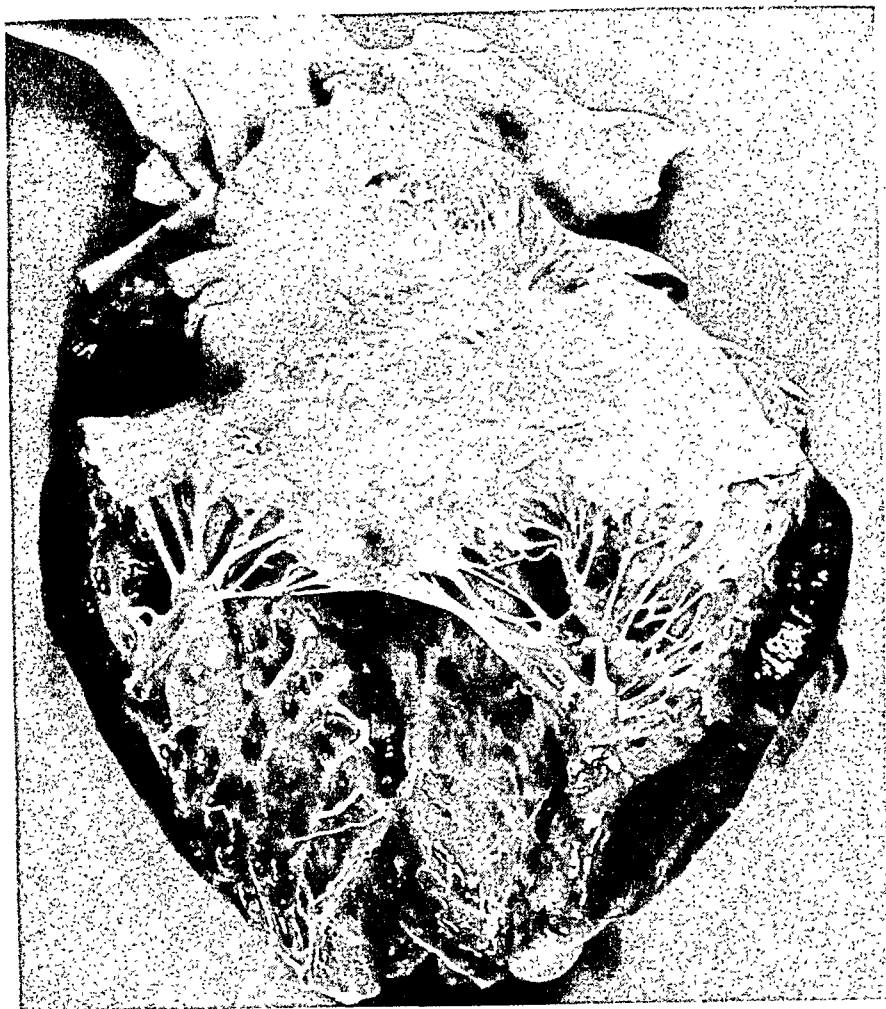


Fig. 1.—Case 1. Endocarditis of mitral valve.



Fig. 2.—Case 1. Photomicrograph of mitral valve with vegetation. H. and E., $\times 8$.

configuration. Electrocardiogram was negative, except for a low T₁. The urinalysis showed albumin, occasional white blood cells, red blood cells, and epithelial cells.

In spite of the sterile blood cultures it was felt that this was nevertheless an advanced case of subacute bacterial endocarditis, and he was started on combined penicillin-heparin therapy. He received a total of 4,900,000 Oxford units of penicillin and 1,350 mg. of heparin over a period of twenty-two days. He was also given digitalis and ammonium chloride because of the advanced myocardial and renal decompensation. Fourteen days after penicillin therapy was started, during which time his condition rapidly deteriorated to the point of cachexia, the patient suddenly went into shock, and despite the administration of two units of human blood plasma, died. During his entire stay at the Jewish Hospital of Brooklyn he had frequent blood cultures, all of which were sterile.

At necropsy* the patient was found to have a thromboulcerative mitral endocarditis; a healed rheumatic endocarditis of the mitral and tricuspid valves (Figs. 1 and 2); a thrombus in the right auricle numerous splenic infarcts (Fig. 3); and infarcts of the kidney, interstitial nephritis, nephrosis, and glomerulitis (Figs. 4 and 5) with adenoma of the left kidney. The myocardium was red-brown in color with grey streaking and was studded with Bracht-Wachter bodies (Fig. 6). He also had erosions of the stomach, urinary bladder, and esophagus, indicative of nutritional insufficiency and avitaminosis. There was also marked generalized emaciation. Cultures taken of all the heart valves were sterile despite the fact that histopathologic section of the affected valves disclosed colonies of organisms in the depths of the vegetations.

CASE 2.—Subacute bacterial endocarditis, recovery with one five-week span of combined penicillin-heparin treatment; post-therapy, nineteen months. Primary rheumatic cardiovalvular lesion of mitral valve.

A. R., a 41-year-old white man, entered the Jewish Hospital of Brooklyn on Oct. 23, 1944, complaining of dyspnea on exertion. He was well until four years prior to admission when he began to complain of temperature, chills, weakness, and fatigue. One year later he had arthralgia of the left knee which was satisfactorily treated with fever therapy and salicylates, but thereafter he ran a very low temperature for four weeks. One year later he had a similar episode affecting the right knee. One year after that he suffered a coronary thrombosis and was in bed for six weeks, following which he had precordial pressure for three to six months. For the ensuing year he had occasional episodes of fever which responded well to sulfamerazine. Six months prior to admission he awoke suddenly complaining of severe pain in the left eye and a petechia was noted on the conjunctival surface.

On admission he was found to be a well-developed, well-nourished white man, who did not appear acutely ill. Examination of the cardiovascular system revealed a regular sinus rhythm with an accentuated apical thrill. There was a systolic murmur and a short presystolic rumble at the apex, especially after exertion, and best heard while lying in the left lateral position. Extremities revealed minimal clubbing of the fingers with subungual splinter hemorrhages.

The electrocardiogram was suggestive of myocardial damage. Repeated blood cultures were sterile, but *Streptococcus viridans* was isolated from the root of an extracted tooth. Despite the protracted history and the persistently sterile blood cultures a diagnosis of subacute bacterial endocarditis was justified because of the cardiac lesion, the temperature, and subungual hemorrhages. He was placed on penicillin and heparin therapy and received a total of 23,700,000 Oxford units of penicillin in dosages varying from 300,000 to 1,000,000 units daily, for a period of five weeks. Four weeks after the beginning of therapy he developed an embolism of the terminal branch of the dorsal arch, analagous to an Osler node, which was painful and very tender. This responded promptly to subcutaneous implants of heparin in the Pitkin menstuum. Upon discharge from the hospital his general condition was excellent; he had no complaints, the cardiac murmurs were less apparent, and there was no splenomegaly. The erythrocyte sedimentation rate was within normal limits. Nineteen months after discharge from the hospital his condition is still excellent and he is able to carry on his customary duties.

*We are indebted to Dr. David M. Grayzel, Acting Director of the Department of Pathology, Jewish Hospital of Brooklyn, for supplying the pathologic data.

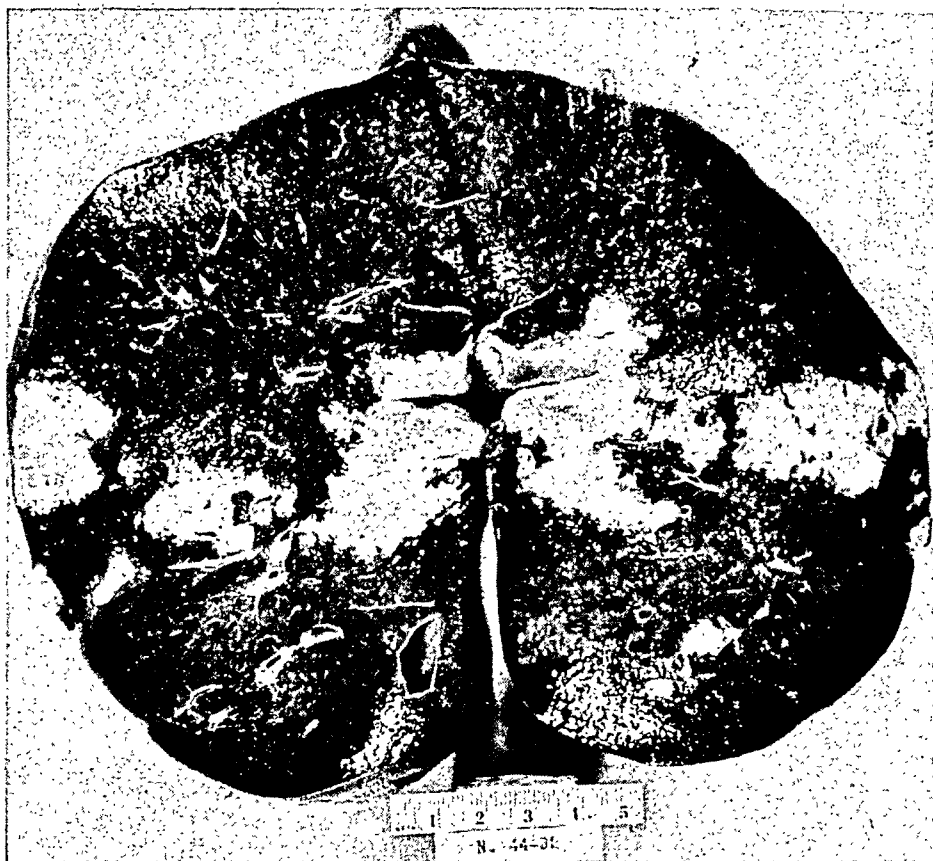


Fig. 3.—Case 1. Cut surface of spleen showing infarcts.



Fig. 4.—Case 1. Photograph of kidney showing infarcts.

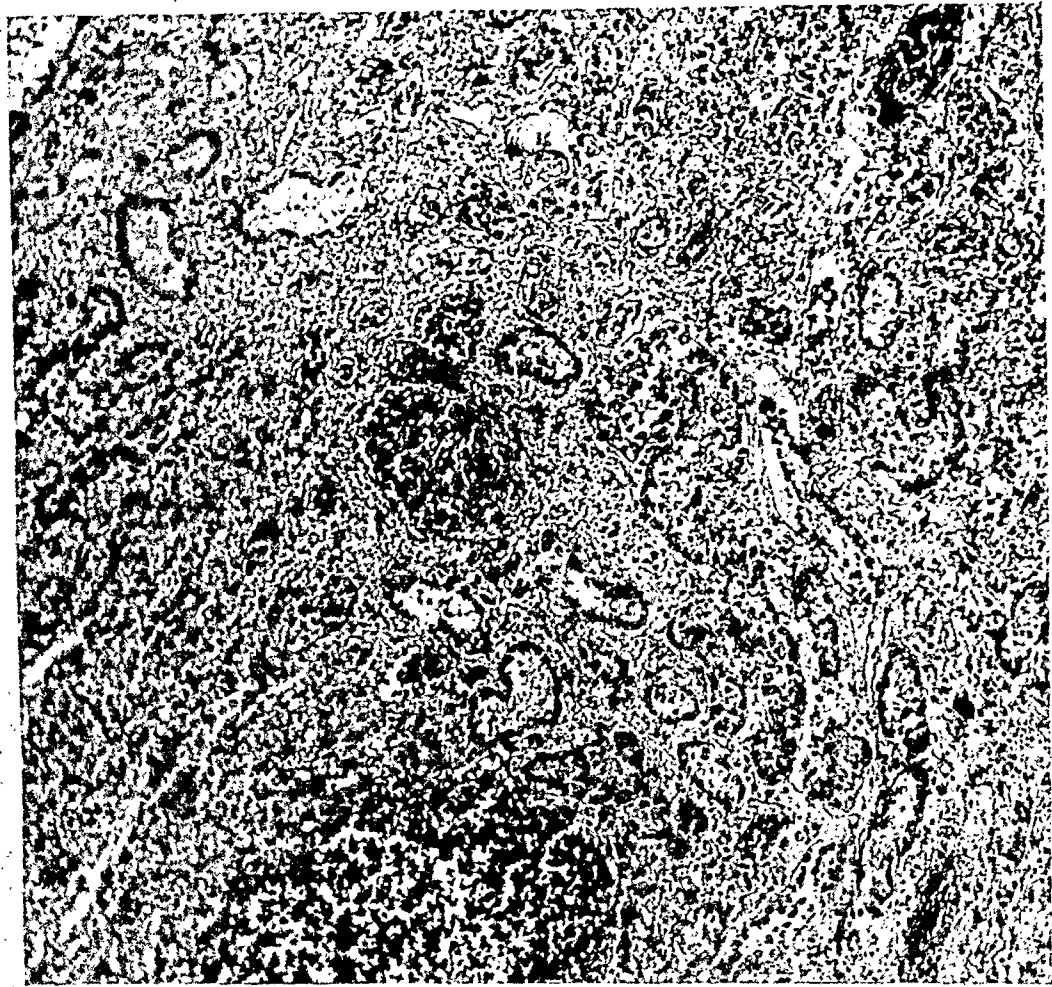


Fig. 5.

Fig. 5.—Case 1. Photomicrograph showing infarct in kidney. H. and E., $\times 220$.

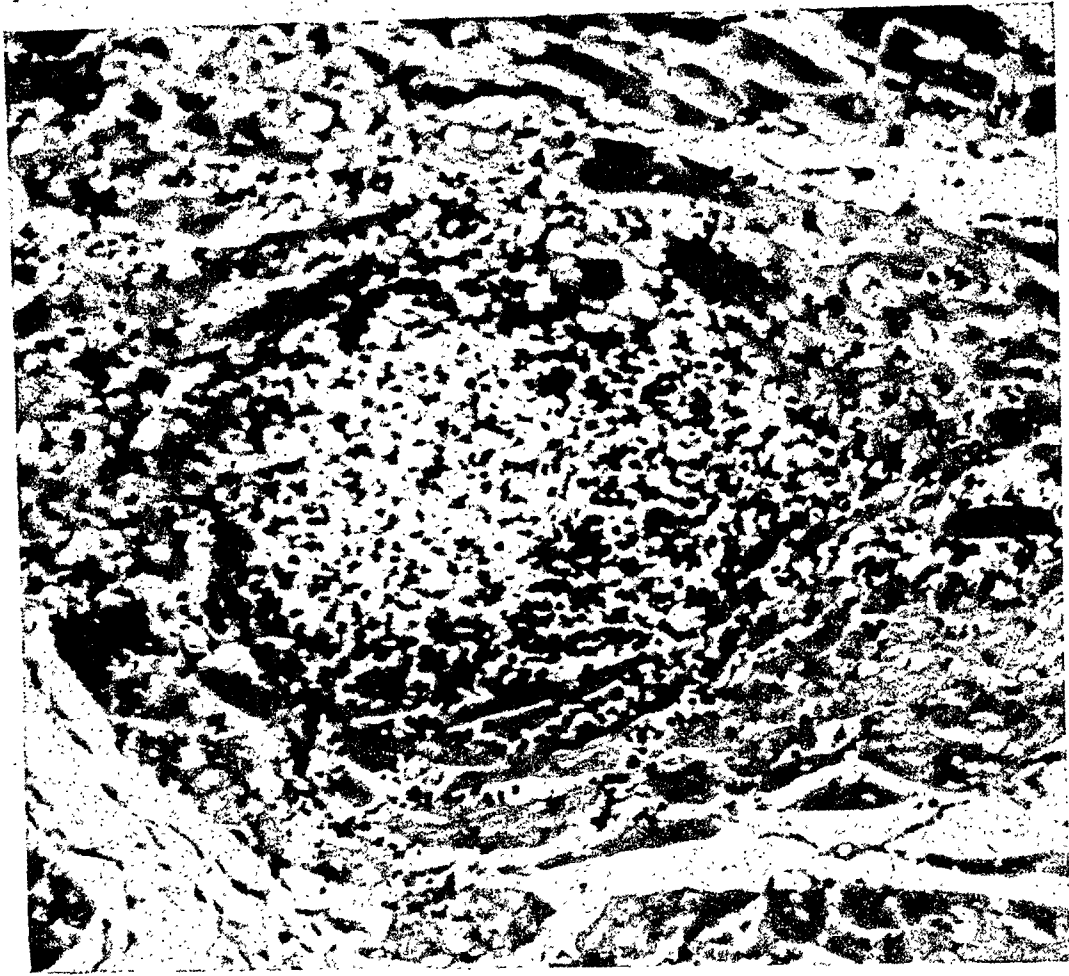


Fig. 6.

Fig. 6.—Case 1. Photomicrograph showing Bracht-Wachter body. H. and E., $\times 210$.

CASE 3.—Subacute bacterial endocarditis, two and one-half months; primary rheumatic cardiovalvular disease of mitral and aortic valves; no response to one three-week course of penicillin intramuscularly; recovery following thirty-six-day span of combined penicillin-heparin therapy: post-therapy, nineteen months.

S. F., a 28-year-old white woman, had temperature and malaise for a period of two and one-half months. At another hospital a diagnosis of subacute bacterial endocarditis was made and she was given penicillin alone intramuscularly for three weeks and then discharged. Five blood cultures taken at that institution were sterile. After five symptomless weeks she again became febrile and was admitted to the Jewish Hospital two days later, on Nov. 21, 1944. There was no past history of any cardiac lesion or rheumatic fever. Cardiac examination disclosed a forceful thrust with systolic thrill and rough systolic murmur at the apex, and a high-pitched, blowing systolic murmur at the aortic area. Splenomegaly and hepatomegaly were present. There was slight cyanosis of the nails with clubbing. No petechiae were observed. The clinical impression was subacute bacterial endocarditis superimposed on rheumatic disease of the mitral and aortic valves. The electrocardiogram disclosed some myocardial damage. All urine specimens showed a faint trace of albumin. All blood cultures were sterile. The patient was given a total of 22,900,000 Oxford units of penicillin and 2,300 mg. of heparin intravenously over a period of thirty-six days, with daily dosages of penicillin ranging from 300,000 to 1,000,000 Oxford units. Nineteen months after discharge patient is well, symptom-free, afebrile, and has returned to her former occupation as a secretary.

CASE 4.—Subacute bacterial endocarditis, four months; primary rheumatic cardiovalvular disease of mitral and aortic valves; infection terminated by two courses of combined penicillin and heparin treatment, twenty-two and thirty-five days respectively; patient succumbed to intractable congestive heart failure. Necropsy showed healed thromboulcerative endocarditic lesions of mutilated aortic and mitral valves; cultures sterile and histopathologic sections negative for bacteria.

S. McF., a 50-year-old white man, entered the Jewish Hospital of Brooklyn on March 22, 1945, complaining of cough and fatigue. Four months prior to admission he had two upper respiratory infections within a three-week period. One month later he had swelling and pain of both ankles and knees, but there was no redness or heat. This was followed by a nonproductive cough and pain in the lumbar region. Two months later he became very easily fatigued and had noticeable loss of strength. This was accompanied by some frequency of urination and precordial pain with palpitation. Two weeks prior to admission he developed a low grade temperature ranging between 100° F. and 102° F., with the peaks occurring at night. He gave no history of rheumatic fever or scarlatina.

On examination he was a well-developed, well-nourished white man who did not appear acutely ill. The heart was enlarged to the left. There was a soft systolic and diastolic murmur over the entire precordial area, radiating to the left axilla and upward to the neck. The rhythm was regular and the blood pressure was 118/100. There was hepatomegaly but no splenomegaly. The fingers were clubbed. Electrocardiogram showed evidence of myocardial damage. Tele-roentgenogram demonstrated a mitralized heart with aortic changes. In spite of the fact that repeated blood cultures were sterile, it was felt that this was a case of subacute bacterial endocarditis engrafted on an old rheumatic valvular defect (mitral and aortic) and combined penicillin-heparin therapy was started. He received an initial course of 2,000,000 Oxford units of penicillin daily, totalling 44,000,000 Oxford units and 2,400 mg. of heparin administered in the Pitkin menstruum for a period of twenty-two days. During this first course of therapy the patient reacted fairly well. However, because of a persistently elevated erythrocyte sedimentation rate it was decided to give a second five-week span of combined therapy, totalling 68,000,000 Oxford units of penicillin and 700 mg. of heparin. Five weeks after this therapy he developed dyspnea and orthopnea and the spleen enlarged to 3 cm. below the costal margin. The heart sounds over the entire precordial area were replaced by a systolic and diastolic murmur, and he developed congestive heart failure of both the backward and forward type. His condition rapidly deteriorated and electrocardiographic studies showed the development of an intraventricular conduction disturbance, with severe myocardial damage and the common type of bundle

branch block. In spite of digitalization and the usual therapeutic measures, the patient died sixteen weeks after admission.

Necropsy, limited to examination of the heart, showed healed thromboulcerative endocarditic lesions of the mitral and aortic valves, the later being bicuspid. The vegetations of the mitral valve were endothelialized and very firm. The chordae tendineae of the mitral valve were thickened and fused. There was also a healed rheumatic endocarditis of this valve (Fig. 7). The aortic valve leaflets were markedly fragmented, the free borders of the valve were frayed, the fragments extending down to the left ventricle (Fig. 8). Cultures of the heart valves were sterile and histopathologic sections of all valves failed to disclose any bacteria. The heart was hypertrophied and markedly dilated. It was apparent that the intractable heart failure was predicated on inability of the heart muscle to accommodate for the severe mutilation of the valves despite the fact that the treatment succeeded in sterilizing the endocarditic lesions.

CASE 5.—Subacute bacterial endocarditis, eleven days; primary congenital heart disease, patent ductus arteriosus; no response to penicillin by fractional intramuscular route; recovery following sixty-six day span of penicillin-heparin treatment; post-therapy, thirteen months.

J. L., a 35-year old white woman, was admitted to the Jewish Hospital of Brooklyn on April 15, 1945, complaining of lower abdominal discomfort, fever, headaches, and ocular pain of eleven days' duration. At the age of three she had had diphtheria, following which her family was informed that she had heart disease. There was no past history of rheumatic infection, scarlet fever, or chorea. On admission, she appeared to be well developed, well nourished, and not in acute distress. Her temperature was 101° F., pulse rate 114 per minute, and blood pressure, 130/70. The cardiac findings were characteristic of patent ductus arteriosus which was confirmed radiographically. There was bilateral costovertebral jar tenderness. There was no splenomegaly or hepatomegaly. The electrocardiogram revealed left ventricular preponderance and myocardial damage. The erythrocyte sedimentation rate was 122 mm. in one hour (Westergren) and the urine showed traces of albumin and the presence of red blood cells. Despite the consistently sterile blood cultures, the clinical impression was subacute bacterial endocarditis engrafted on a patent ductus arteriosus with embolization to the kidneys. The patient was placed on a treatment program consisting first of sulfonamides and then of penicillin given by the fractional intramuscular method. Her condition became progressively worse, the presenting clinical feature being repeated pulmonary embolization with consequent massive infarction and consolidation. She was then referred for intensive therapy which was begun with a dosage plan of 500,000 Oxford units of penicillin and 100 mg. of heparin by continuous venoclysis. It was not, however, until the daily penicillin dose was increased first to 2,000,000, then to 5,000,000, and finally to 10,000,000 Oxford units that the response was satisfactory and the infection controlled. After a rather stormy course, during which time the patient received a total of 215,000,000 Oxford units of penicillin and 2,500 mg. of heparin over a period of sixty-six days, the clinical condition improved considerably, the symptoms disappeared, temperature became normal, and the erythrocyte sedimentation rate receded to 19 mm. in one hour. She was discharged from the hospital on Oct. 21, 1945, and is now completely recovered and carrying on with her activities as housewife.

CASE 6.—Subacute bacterial endocarditis, five months; primary rheumatic cardiovalvular disease of mitral and aortic valves; infection terminated by one twenty-two-day span of penicillin-heparin therapy; succumbed to coronary artery thrombosis nine months post-therapy.

A. S., a 42-year-old white man, was admitted to the Jewish Hospital of Brooklyn on June 25, 1945, complaining of migratory polyarthritides and low grade temperature for a period of five months. The pyrexial periods were preceded by chilly sensations, but no actual shaking chills. The skin presented transitory crops of painful lesions (embolic), lasting from twenty-four to thirty-six hours. One week prior to admission, he developed a nonproductive cough. There was no past cardiac history.

On admission he was found to be an acutely ill man with marked pallor. The teeth were in poor dental condition. He had a sinus tachycardia and a Corrigan pulse. The heart was enlarged to the left and to the right. The first sound at the base was replaced by a loud systolic



Fig. 7.—Case 4. Endocarditis of mitral valve. Note thickening of valve cusps and chordae tendineae.

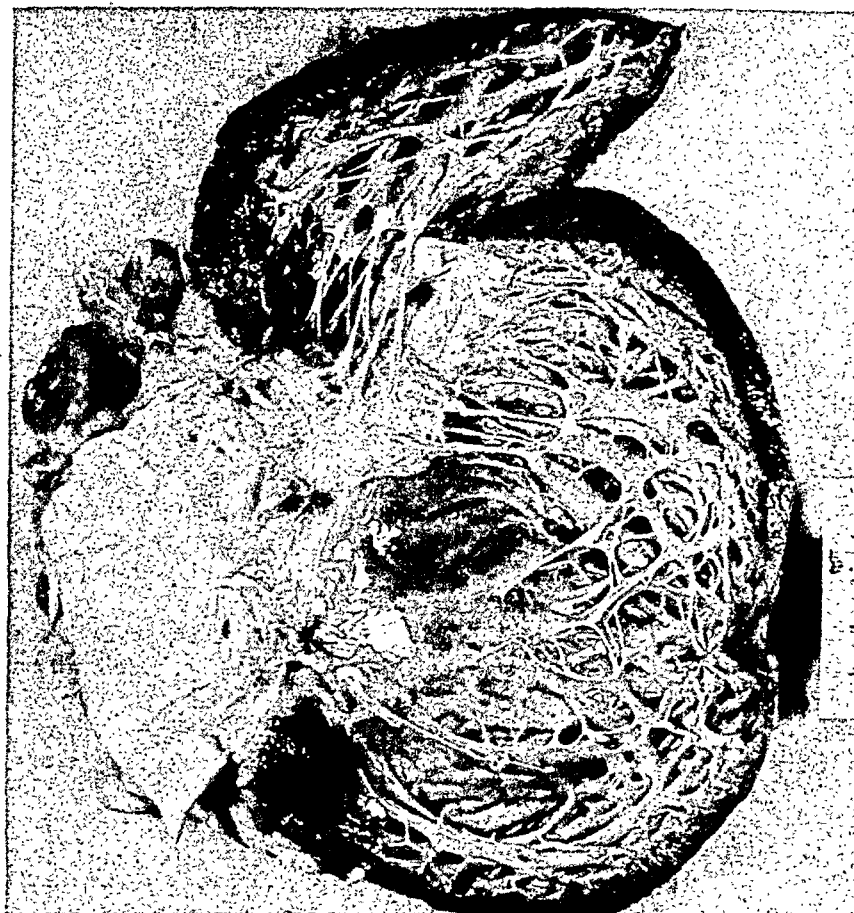


Fig. 8.—Case 4. Endocarditis of aortic valve.

murmur, best heard at Erb's point. The liver was enlarged 5 cm. below the costal margin and the edge was tender. Splenomegaly measured 3 cm. below the costal margin. There was marked bilateral clubbing of the fingers. The left ankle was markedly tender, red, and swollen. Petechiae were present on the left large toe and on the medial aspect of the left heel. The clinical impression was polyarthritis, aortic insufficiency, and aortic stenosis, with mild congestive failure, and superimposed subacute bacterial endocarditis. Blood cultures taken for three consecutive days and weekly thereafter were sterile. Electrocardiogram revealed myocardial damage and a prolongation of the P-R interval to 0.32 second. The hemogram showed 58 per cent hemoglobin, 3.11 million red blood cells, 8,400 white blood cells with 75 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 7 per cent monocytes.

Because of the poor condition of the patient, and despite the sterile blood cultures, he was placed on massive penicillin-heparin therapy. During the course of treatment he had petechias of the right foot, a right renal infarct, and right saphenous vein thrombophlebitis. The latter two were cleared up without residue by subcutaneous injections of heparin in the Pitkin menstruum. After twenty-two days of treatment, using 500,000 Oxford units of penicillin daily intravenously and totaling 11,000,000 Oxford units, the patient became afebrile, asymptomatic, and ambulatory.

The patient remained well for nine months when he was readmitted to the hospital in acute heart failure with pulmonary edema. This developed suddenly on the evening of admission. The acute heart failure was probably due, as evidenced by the electrocardiogram, to early posterior wall infarction superimposed on an old anterior wall infarction. There was no indication of any recurrent bacterial endocarditis. The patient died suddenly seven days after admission. No autopsy was obtained. The final diagnoses were (1) acute left ventricular failure with pulmonary edema (coronary occlusion), (2) rheumatic heart disease, and (3) healed subacute bacterial endocarditis.

CASE 7.—Subacute bacterial endocarditis, two months; primary atherosclerotic cardiovascular disease; successful response to thirty-five-day span of penicillin-heparin treatment; post-therapy, eight months.

M. S., a 48-year-old white man, was admitted to the Jewish Hospital of Brooklyn on Aug. 8, 1945, complaining of migratory polyarthritis which had been present for a period of two months. Five weeks prior to admission he developed a sore throat with temperature and was treated with sulfonamides and penicillin. For the previous three weeks he had a continuous low grade temperature, increasing fatigability, and loss of weight.

Examination revealed a well-developed, well-nourished white man who did not appear acutely ill. The clinical findings justified a diagnosis of subacute bacterial endocarditis superimposed on an atherosclerotic cardiovascular lesion. He had minimal clubbing of the fingers. Blood pressure was 120/92. Teleroentgenogram revealed left ventricular enlargement; and the electrocardiogram, left axis deviation. The erythrocyte sedimentation rate was 67 mm. in one hour (Westergren) and urinalyses showed faint traces of albumin and occasional white blood cells. Repeated blood cultures were sterile. He was started on 500,000 Oxford units of penicillin daily by vein, with heparin, and given a thirty-five-day span of treatment totaling 17,500,000 Oxford units of penicillin and 2,700 mg. of heparin. He responded promptly, became progressively better, and although the sedimentation rate remained slightly elevated, he was discharged from the hospital as a recovered case.

CASE 8.—Subacute bacterial endocarditis, four months; primary rheumatic cardiovalvular disease of the mitral valve; unsuccessful response to prolonged, intensive, massive penicillin-heparin therapy; recovery following forty-six days of streptomycin; post-therapy, eight months.

E. L. S., a 25-year-old white woman, was well until four years prior to her present illness. At that time she was told that she had a "bad heart" (rheumatic heart disease). Four months prior to admission, following an upper respiratory infection, the patient developed a persistent fever associated with chills, malaise, and pallor. Numerous blood cultures, aerobic and anaerobic, were consistently sterile. Six days after admission to another hospital, on Aug. 30, 1945, she developed splenomegaly and began to deteriorate. The temperature ranged between 103° F.

and 105° F. and the clinical picture seemed typical of subacute bacterial endocarditis. The patient, therefore, was started on penicillin-heparin therapy and after four days the temperature characteristically dropped and she improved greatly. However, despite intensification of the therapy, the temperature recurred and her condition rapidly became worse. She was then transferred to the Jewish Hospital of Brooklyn where after a comprehensive clinical and laboratory survey all alternative diagnoses were again excluded. The daily dosage plan of penicillin was stepped up to five million Oxford units and then to ten million Oxford units without significant response. Repeated blood cultures were sterile. The temperature continued to spike and the hemic component remained low in spite of numerous blood transfusions. On the one hundred thirtieth day of her illness, the spleen became markedly enlarged and although splenic and sternal marrow punctures were negative, the possibility of Hodgkin's disease was considered. Probationary x-ray therapy was instituted but was discontinued because of the failure of response. Penicillin therapy was again started, using 10,000,000 Oxford units daily with heparin. Her clinical condition continued to regress to such an extent that she lost approximately 60 pounds in weight, had complete anorexia, and death was expected momentarily. On the one hundred sixtieth day of her illness, streptomycin therapy was added to the program. It was given intramuscularly because of the presence of pyrogens which contraindicated its intravenous use. Forty-eight hours after streptomycin therapy was begun the temperature receded to 101° F., her appetite increased, and her general condition improved remarkably. It was decided to continue with streptomycin alone. During the forty-six days of streptomycin therapy, a total of 57.5 Gm. (57,500,000 units) were given in dosages ranging from 1 to 2 Gm. daily. While on this therapy, the appetite increased greatly and the patient gained some 35 pounds in weight. She is now eight months post-therapy, completely afebrile, and ambulatory. She now weighs 150 pounds, which represents a total gain of 40 pounds, the hemoglobin is 82 per cent, and the erythrocyte sedimentation rate is 7 mm., as contrasted with a high of 117 mm. in one hour (Westergren) during the active illness.

CASE 9.—Subacute bacterial endocarditis, one year; primary rheumatic cardiovalvular disease of the mitral valve; two courses of penicillin alone of twenty-one and forty days, respectively, failed to terminate the infection; successful response to one fifty-three-day span of combined penicillin-heparin treatment; post-therapy, four months.

L. G., a 44-year-old white woman, who was admitted to the Jewish Hospital of Brooklyn on April 9, 1946, had developed intermittent and irregular temperature one year prior to admission. The temperature, cardiac lesion, splenomegaly, and petechiasis of the fingers justified a diagnosis of subacute bacterial endocarditis superimposed on a rheumatic cardiovalvular defect (mitral stenosis). Despite the repeatedly sterile blood cultures, in May, 1945, at another institution, she received a three-week span of treatment with penicillin by fractional intramuscular method totalling 3,675,000 Oxford units. This therapy resulted in the disappearance of all symptoms. Her symptoms returned and the patient was retreated in June, 1945, receiving a total of 54,400,000 Oxford units intramuscularly over a period of forty days. She was discharged afebrile and improved, though with persistent splenomegaly.

On admission to the Jewish Hospital, she appeared well developed, well nourished but pallid, and chronically ill. Cardiac findings indicated a double mitral lesion which was confirmed radiographically. Hepatomegaly and splenomegaly were 5 cm. and 3 cm., respectively, below the costal margin. Blood pressure was 130/80. Electrocardiogram showed simple P-R prolongation and myocardial damage. Repeated blood cultures were sterile. Erythrocyte sedimentation rate was 118 mm. in one hour (Westergren) and the urine contained occasional white and red blood cells.

She became afebrile on combined penicillin and heparin treatment. The secondary anemia was combatted with repeated blood transfusions and hematinics. The total penicillin given was 228,000,000 Oxford units over a period of fifty-three days, with a total of 3,800 mg. of heparin. At the completion of this therapy, while ambulatory, the patient developed thrombophlebitis of the left lower extremity which responded to seven deposits of heparin, given in the Pitkin menstruum over a period of fourteen days, and totalling 2,300 milligrams. She is now four months post-therapy and continues to fulfill the criteria of a recovered case.

CASE 10.—Subacute bacterial endocarditis, six weeks; primary rheumatic cardiovalvular disease of the mitral valve; recovery following one forty-one-day span of combined penicillin-heparin treatment; post-therapy; four months.

L. R., a 20-year-old white man, was admitted to the Jewish Hospital of Brooklyn on April 19, 1946. He had had rheumatic heart disease at the age of 2 years but remained well until six weeks prior to admission. Since then he had recurrent temperature with and without chills, aching joints, and sore spots in various sites.

On admission the important cardiac finding was a blowing systolic murmur at the apex referred all over the precordium. Hepatomegaly was 2 cm. below the costal margin. Blood pressure was 125/80. Electrocardiogram disclosed mild myocardial damage. Erythrocyte sedimentation rate was 15 mm. in one hour. (Patient had had some penicillin treatment before admission to the hospital.) The blood cultures were all sterile. The diagnosis was subacute bacterial endocarditis engrafted on a rheumatic valvular defect and intensive penicillin-heparin therapy was begun. Because of the preadmission subcurative penicillin therapy, a minimum daily dosage of 2,000,000 Oxford units was indicated. Due to lack of prompt response, this was immediately increased to 5,000,000 units. He was given a total of 182,000,000 units in forty-one days, with a total of 2,500 mg. of heparin. He is now four months post-therapy and is considered a recovered case.

CASE 11.—Subacute bacterial endocarditis, five months; primary rheumatic cardiovalvular disease of the mitral valve; cerebral embolus; recovery following one thirty-six-day span of combined penicillin-heparin treatment; post-therapy, four months.

H. W., a 51-year-old white woman, was admitted to the Jewish Hospital of Brooklyn on May 24, 1946, with a five-month history of night sweats, chills, fever, and debility. She had cough, hemoptysis, and clubbing of the fingers. Twenty-five years ago she was told she had rheumatic heart disease. For the past one and one-half years she has had dyspnea on exertion.

On admission she presented the typical findings of mitral rheumatic disease with auricular fibrillation. Hepatomegaly was 3 cm. below the costal margin, but the spleen was not palpable. There were petechiae on the abdomen. Blood pressure was 105/80 and temperature was 102° Fahrenheit. Teleroentgenogram was typical of mitral regurgitation. Electrocardiogram revealed auricular fibrillation and myocardial damage. The blood cultures were all sterile. Urine showed occasional red and white blood cells.

Four days after admission the patient almost expired following a left cerebral embolus complicated by shock and myocardial failure. Aside from this, the response to combined penicillin-heparin therapy was uneventful. This was given over thirty-six days and required a total of 97,000,000 Oxford units of penicillin, with 1,300 mg. of heparin. She is now four months post-therapy and is completely free of any bacterial endocarditic activity.

DISCUSSION

The classical symptoms and signs of subacute bacterial endocarditis include chills, fever, diaphoresis, emaciation, splenomegaly, various cardiac symptoms, renal disturbances, tender cutaneous lesions, petechiae, Osler nodes, purpura, pulmonary symptoms, sternal tenderness, cafe-au-lait expression, joint and ocular changes, and central nervous system embolic phenomena. However, the clinical diagnosis of subacute bacterial endocarditis is generally accepted when only the following manifestations are evident: a past history of rheumatic fever with resultant cardiovalvular defect or the presence of congenital heart disease; an insidious onset with lassitude, weakness, anorexia, and low grade fever; cutaneous or visceral embolization; and splenomegaly.

The diagnosis of subacute bacterial endocarditis is authenticated when, in addition to the preceding, the blood culture is repeatedly positive, the infecting

organism being preponderantly the nonhemolytic type of streptococcus. With persistence and proper techniques, positive blood cultures can be obtained in 85 to 95 per cent of cases.

It is evident from a review of the case histories (Table I) that these eleven patients presented the customary protean clinical manifestations which typify this disease. Apart from the sterile blood cultures, all of the requisite diagnostic criteria were fulfilled. All had primary cardiac lesions, nine rheumatic, one congenital, and one atherosclerotic; all had prolonged fever of varying degree, and eight (73 per cent) had embolic phenomena and/or splenomegaly.

The blood cultures were repeatedly sterile in all eleven patients despite assiduous efforts to identify the infecting organism. The designated diagnosis of subacute bacterial endocarditis of undetermined origin, therefore, is justified for the entire series. Two patients who succumbed and were necropsied (Cases 1 and 4) had three and twelve sterile blood cultures, respectively, and yet had typical thromboulcerative endocarditis as shown grossly and histopathologically. Significantly, no bacteria could be recovered from the blood or vegetations of Case 1, although organisms were observed in microscopic sections of the patently active endocarditic lesions. The etiological agent either was not recoverable by the elaborate techniques which were employed or was destroyed by native or circulating antibodies. These patients who came to necropsy and presented the typical pathologic picture of subacute bacterial endocarditis would tend to document the entire series because the same rigid diagnostic criteria were employed in all eleven patients.

One of the patients (Case 4) suffered severe intractable myocardial failure associated with the common type of bundle branch block. He deteriorated rapidly because of the progressive cardiac damage and apparently did not survive long enough to receive the lasting benefits from the combined therapy, although the vegetations at necropsy appeared healed. Case 6 also presented the picture of irremediable heart failure of the type seen occasionally following successful treatment of the bacterial endocarditis and now known to be due to severe mutilation of the valves. The clinical and pathologic aspects of this syndrome have been published.⁸

Case 1 was admitted to the hospital in a greatly emaciated and exhausted condition. He appeared cachectic and presented evidences of advanced myocardial and renal disease and a well-developed avitaminosis. This patient was our only frank treatment failure because it was not possible to give him the prolonged therapy needed in these deteriorated patients. Of the entire group of eleven patients this patient most nearly portrayed the clinical picture of the bacteria-free stage described by Libman and Friedberg.⁹ If the mechanism of the bacteria-free stage of subacute bacterial endocarditis is the protracted destruction of bacteria with consequent liberation of noxious bacterial proteins one may still conceivably encounter an occasional patient with this classical syndrome who did not receive the benefits of therapy, either because of failure of diagnosis or the use of subcurative doses of the anti-infective agent. If, on the other hand, the so-called bacteria-free stage is merely an active phase of sub-

TABLE I. CLINICAL FEATURES IN SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

CASE	SEX	AGE	CARDIAC PRIMARY LESION	DURATION OF ILLNESS (MONTHS)	ONSET WITH UPPER RES- PIRATORY INFECTION	FEVER	EMBOLIC PHENOMENA	SPLE- NOMEGALY	ANEMIA	ARTH- RALGIA	STERILE BLOOD CULTURES (NUMBER)
(1) C.M.T.	M	48	Rheumatic	18	Yes	Yes	Yes	Yes	Yes	No	3
(2) A.R.	M	41	Rheumatic	48	Yes	Yes	Yes	Yes	No	Yes	7
(3) S.F.	F	28	Rheumatic	2½	Yes	Yes	No	Yes	Yes	No	15
(4) S.M.F.	M	50	Rheumatic	4	Yes	Yes	No	No	No	Yes	12
(5) J.L.	F	35	Congenital	1½	Yes	Yes	Yes	No	Yes	Yes	14
(6) A.S.	M	42	Rheumatic	5	No	Yes	Yes	Yes	Yes	Yes	11
(7) M.S.	M	48	Atherosclerotic	2	Yes	Yes	No	No	No	Yes	7
(8) E.L.S.	F	25	Rheumatic	4	Yes	Yes	Yes	Yes	Yes	No	20
(9) L.G.	F	44	Rheumatic	12	No	No	Yes	Yes	Yes	Yes	18
(10) L.R.	M	20	Rheumatic	1½	Yes	Yes	Yes	No	No	Yes	11
(11) H.W.	F	51	Rheumatic	5	Yes	Yes	Yes	No	Yes	No	5

acute bacterial endocarditis wherein the bacterial agent can not be identified or isolated, fewer of these patients should be encountered as more of them are properly catalogued and given the benefit of curative therapy.

Of the eleven cases, ten (91 per cent) were considered to have been successfully treated, clinically arrested, or cured (Table II). Because of the lack of a recoverable infecting organism, a treatment program predicated on its behavior in the test tube could not be planned. It was necessary, therefore, to conduct the treatment on a trial and error basis by observation of the clinical response. As a result, some of the patients were placed on our minimum standard program of 500,000 Oxford units daily for five weeks with requisite doses of heparin. If they did not respond favorably, that is to say, if the temperature did not fall promptly within a week and the splenomegaly did not begin to recede, or there was a persistence of embolic phenomena, it was obvious that the dosage schedule was inadequate and the treatment was therefore intensified. There was no hesitancy in revising the penicillin dosages upward rapidly to two million units a day, five million units a day, and even, in Case 8, to ten million units a day. Of the eleven patients, four responded successfully to one span of treatment of three to six weeks, requiring an average of 18 million units of penicillin. Case 5 finally responded satisfactorily after her daily penicillin dosage was increased to five million units. She required nine and one-half weeks of treatment totaling 215,000,000 units of penicillin. Case 8 did not respond to prolonged and repeated courses of penicillin therapy. Finally, as a last resort this patient was placed on streptomycin therapy to which she responded spectacularly and is now considered cured. The recovery rate of 91 per cent for this series of eleven patients parallels the expected and anticipated recovery rate in similarly treated cases of subacute bacterial endocarditis infected with nonhemolytic type of streptococcus.

On the basis of the foregoing, in order to terminate the infection under optimum conditions it is imperative to give an adequate span of the therapy as soon as the diagnosis is suspected, even before the results of the blood cultures are known. Ideally, the treatment program in subacute bacterial endocarditis should be based on the identity and test tube behavior of the infecting organism. However, in order to save valuable time, minimize the hazard of serious embolization, and obviate excessive damage to the cardiovalvular apparatus, it is inadvisable to await an unequivocal laboratory confirmation.

A successful outcome in the absence of a positive blood culture serves to confirm an otherwise valid clinical diagnosis of subacute bacterial endocarditis. Very few diseases can be confused with this clinical syndrome which would respond so favorably to this type of therapy. In this connection, the most common diagnostic problem is the differentiation between rheumatic fever and subacute bacterial endocarditis, particularly when they coexist. In actual practice, when confronted with a clinical syndrome wherein the diagnosis rests between subacute bacterial endocarditis and rheumatic fever, a probationary trial of penicillin treatment should be prescribed. The diagnosis resolves itself usually within a week: if the patient has subacute bacterial endocarditis there is appreciable clinical improvement accompanied by recession in temperature; if, however, the patient should have active rheumatic fever, the clinical manifestations re-

TABLE II. TREATMENT PROGRAM AND RESULTS IN SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

CASE	PREVIOUS TREATMENT	DURATION TREATMENT (WEEKS)	TOTAL PENICILLIN OXFORD UNITS (MILLION)	TOTAL HERAPIN (MG.)	STREPTOMYCIN (GRAMS)	POST-THERAPY OBSERVATIONS (MONTHS)	RESULTS	REMARKS
(1) C. M. T.	Sulfa	3	4.9	1350	None		Failure	Death due to inanition, avitaminosis, cultures of lesions sterile, organisms in microscopic sections of active lesions
(2) A. R.	Typhoid vaccine, sulfa	5	23.7	2100	None	19	Successfully treated	
(3) S. F.	Penicillin	5	22.9	2300	None	19	Successfully treated	
(4) S. M. F.	Penicillin	8	112.0	3100	None		Successfully treated	Died of cardiac decompensation. No organisms in cultures or microscopic sections of healed lesions
(5) J. L.	Sulfa, penicillin	10	215.0	2500	None	13	Successfully treated	
(6) A. S.	None	3	11.0	1100	None	9	Successfully treated	Died 9 months post-therapy of coronary occlusions, left ventricular failure
(7) M. S.	Sulfa	5	17.5	2700	None	8	Successfully treated	
(8) E. L. S.	None	30	250.0	5400	57.5	8	Successfully treated	
(9) L. G.	Penicillin	8	228.0	6100	None	4	Successfully treated	Post-therapy thrombophlebitis cured with subcutaneous heparin Pitkin menstruum
(10) L. R.	Penicillin	6	182.0	2500	6.0	4	Successfully treated	
(11) H. W.	None	5	97.0	1300	4.0	4	Successfully treated	

main static or may, in fact, become aggravated. It has been our experience, as well as that of others,^{10,11} that rheumatic fever patients do not fare well in the face of penicillin therapy. We have come to rely on the response to this probationary span of treatment as a differential diagnostic aid.

SUMMARY AND CONCLUSIONS

1. Eleven patients with clinically authentic subacute bacterial endocarditis are reported in whom blood cultures were sterile despite repeated efforts. They represent almost 7 per cent of a total of 166 patients with subacute bacterial endocarditis admitted for treatment with the combination of penicillin and heparin.

2. Of the eleven patients, ten (91 per cent) were successfully treated. Of these ten, nine responded favorably to the conjoint penicillin and heparin therapy. In the tenth patient the infection was finally terminated by streptomycin, after the combination of penicillin and heparin had failed to accomplish this result. Two of the patients who were successfully treated subsequently succumbed to intractable heart failure. One of these patients who came to necropsy presented valves so mutilated as to be incompatible with life. No bacteria could be recovered from the healed valves nor could any organisms be seen in histopathologic sections.

3. One patient who succumbed proved upon necropsy to have had the typical pathologic picture of active subacute bacterial endocarditis. No organism could be recovered from the thromboulcerative endocardial lesions although organisms were observed in histopathologic preparations.

4. As a result of observations in this series of eleven patients, it is apparent that these cases should be treated as promptly and intensively as though they had positive blood cultures. The satisfactory response to treatment serves as a differential diagnostic aid.

We wish to thank Mr. John L. Smith of Chas. Pfizer & Company, Inc., for the generous supplies of penicillin and streptomycin used in the treatment of these patients.

REFERENCES.

1. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis—Report of Seven Consecutive Successfully Treated Patients, *J. A. M. A.* 124:144, 1944.
2. Loewe, L.: The Combined Use of Anti-infectives and Anticoagulants in the Treatment of Subacute Bacterial Endocarditis, *Bull. New York Acad. Med.* 21:59, 1945.
3. Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis, *Canad. M. A. J.* 52:1, 1945.
4. Loewe, L., Rosenblatt, P., and Greene, H. J.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, *Bull. New York Acad. Med.* 22:270, 1946.
5. Conferences on Therapy: The Treatment of Subacute Bacterial Endocarditis (Departments of Pharmacology and Medicine, Cornell University Medical College and New York Hospitals, Jan. 11, 1945), *New York State J. Med.* 45:1452, 1945.
6. Loewe, L., Plummer, N., Niven, C. F., Jr., and Sherman, J. N.: A Hitherto Undescribed Variety of Non-hemolytic Streptococcus Recovered from Patients With Subacute Bacterial Endocarditis, *J. A. M. A.* 130:257, 1946.
7. Loewe, L., and Altire-Werber, E.: The Clinical Manifestations of Subacute Bacterial Endocarditis Caused by Streptococcus S.B.E., *Am. J. Med.* 1:353, 1946.

8. Rosenblatt, P., and Loewe, L.: Healed Subacute Bacterial Endocarditis, *Arch. Int. Med.* 76:1, 1945.
9. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, (Edited by Henry A. Christian; reprinted from Oxford Loose-Leaf Medicine), London, 1941, Oxford University Press, pp. 59-76.
10. Watson, R. F., Rothbard, S., and Swift, H. F.: The Use of Penicillin in Rheumatic Fever, *J. A. M. A.* 126:274, 1944.
11. Foster, F. P., McEachern, G. C., Miller, J. H., Ball, F. E., Higley, C. S., and Warren, H. A.: The Treatment of Acute Rheumatic Fever With Penicillin, *J. A. M. A.* 126:281, 1944.

AURICULAR FIBRILLATION WITH ABERRATION SIMULATING VENTRICULAR PAROXYSMAL TACHYCARDIA

JAMES L. GOUAUX, M.D., AND RICHARD ASHMAN, Ph.D.
NEW ORLEANS, LA.

THE term *aberration* has been defined by Lewis as the "abnormal distribution of a supraventricular impulse in the ventricle." This abnormal distribution of impulses, according to the same author, is due to "defects in conduction through some of the chief Purkinje strands." Lewis¹ illustrates the usually permanent aberration of bundle branch block and the aberration confined to the single ventricular response to a premature beat of supraventricular origin; and he calls attention to aberration in auricular fibrillation, in auricular flutter, and in certain cases of supraventricular tachycardia. One case of the latter type was a child. The auricular rate was about 290 per minute, and occasionally a supraventricular impulse was blocked. On one part of the graphic record, the QRS complex after the pause caused by the blockage was of the usual, narrower form, but the next six complexes were wide. Another beat was dropped; the next QRS complex was narrow; the following complex displayed aberration, but it was not so much deformed as the other wide complexes; and the subsequently appearing complexes were again of the usual, narrower form.

Many other examples of aberration have appeared in the literature, including those seen in supraventricular paroxysmal tachycardia which may simulate ventricular tachycardia. Particularly noteworthy, perhaps, is a patient, described by Barker, Johnston, and Wilson,² who had sinus tachycardia and who developed right bundle branch block on two occasions after the administration of quinidine. A very interesting case, similar to ours, was described by Miller.³ The electrocardiogram of his patient, who had an infarct in the interventricular septum and who died while records were being taken, showed auricular fibrillation. At times the ventricular rate was as high as 185 per minute, without aberration. On other parts of the record, with little change in rate, right bundle branch block was seen. At other times the wide complexes were changed in form, and the author attributed this to ventricular paroxysmal tachycardia. Since the rhythm was unchanged during these paroxysms, we offer the unprovable alternative suggestion that these greatly deformed QRS complexes may be due to a combination of complete right bundle branch block and block in most of the subdivisions of the left bundle branch.⁴

The Heart Station, the Charity Hospital of Louisiana at New Orleans, and the Department of Physiology, Louisiana State University School of Medicine.

Received for publication Dec. 23, 1946.

CASE REPORT

The patient whose electrocardiograms are here presented was a 48-year-old Negro man, whose clinical diagnosis was thyrotoxicosis. He had auricular fibrillation, his blood pressure was 120/80. No clinical evidence of organic heart disease could be found. In this case quinidine was administered in an attempt to stop the fibrillation. The case is presented because it shows periods when the ventricular rate is high, about 200 beats per minute, but with no aberration; and other periods when, with no greater ventricular rate, many successive complexes are of the right bundle branch block type. We believe this case gives information in regard to the mechanism whereby the aberrant complexes, once they appear, are maintained.

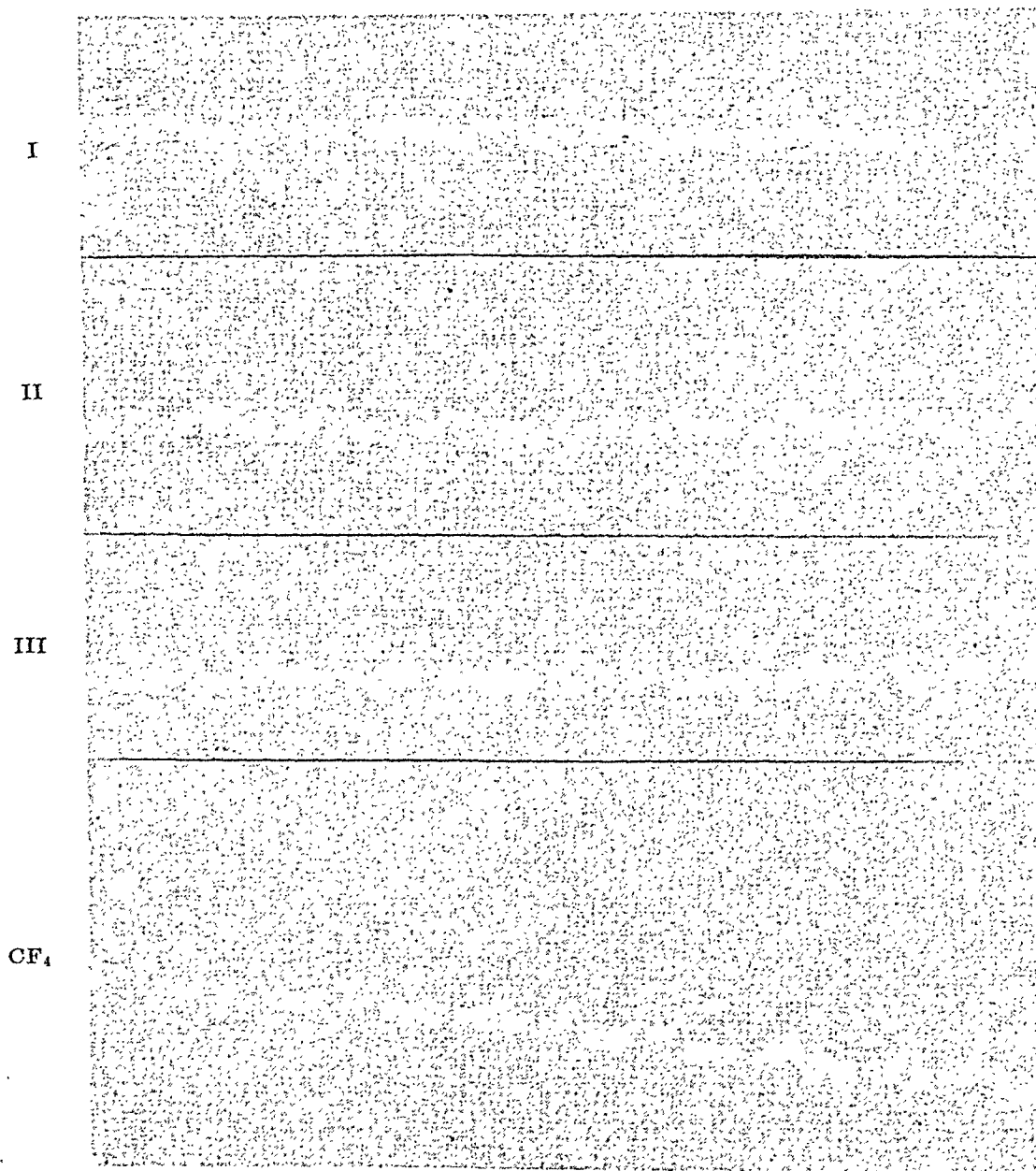


Fig. 1.—Leads I, II, III, and CF_4 taken shortly before the administration of quinidine. Auricular fibrillation with slight aberration shown by the QRS complexes when short ventricular cycles follow relatively long ones.

The Electrocardiographic Findings.—Fig. 1 is the electrocardiogram of this patient taken at 9:25 A.M., shortly before the administration of quinidine. It is a typical example of auricular fibrillation. Two electrocardiograms taken five

and six months previously were similar, except the ventricular rate was not so high. A minimal or slight change is observed to take place in the QRS complexes ending short cycles when these follow long ventricular cycles. Three grains of quinidine sulphate were then administered. Fig. 2 is the electrocardiogram taken at 11:00 A.M., about an hour and a half later. No appreciable change other than a slight slowing has occurred in the auricular complexes. The average ventricular rate is slightly greater. Consistently, throughout this electrocardiogram, when short ventricular cycles follow relatively long cycles, or when very

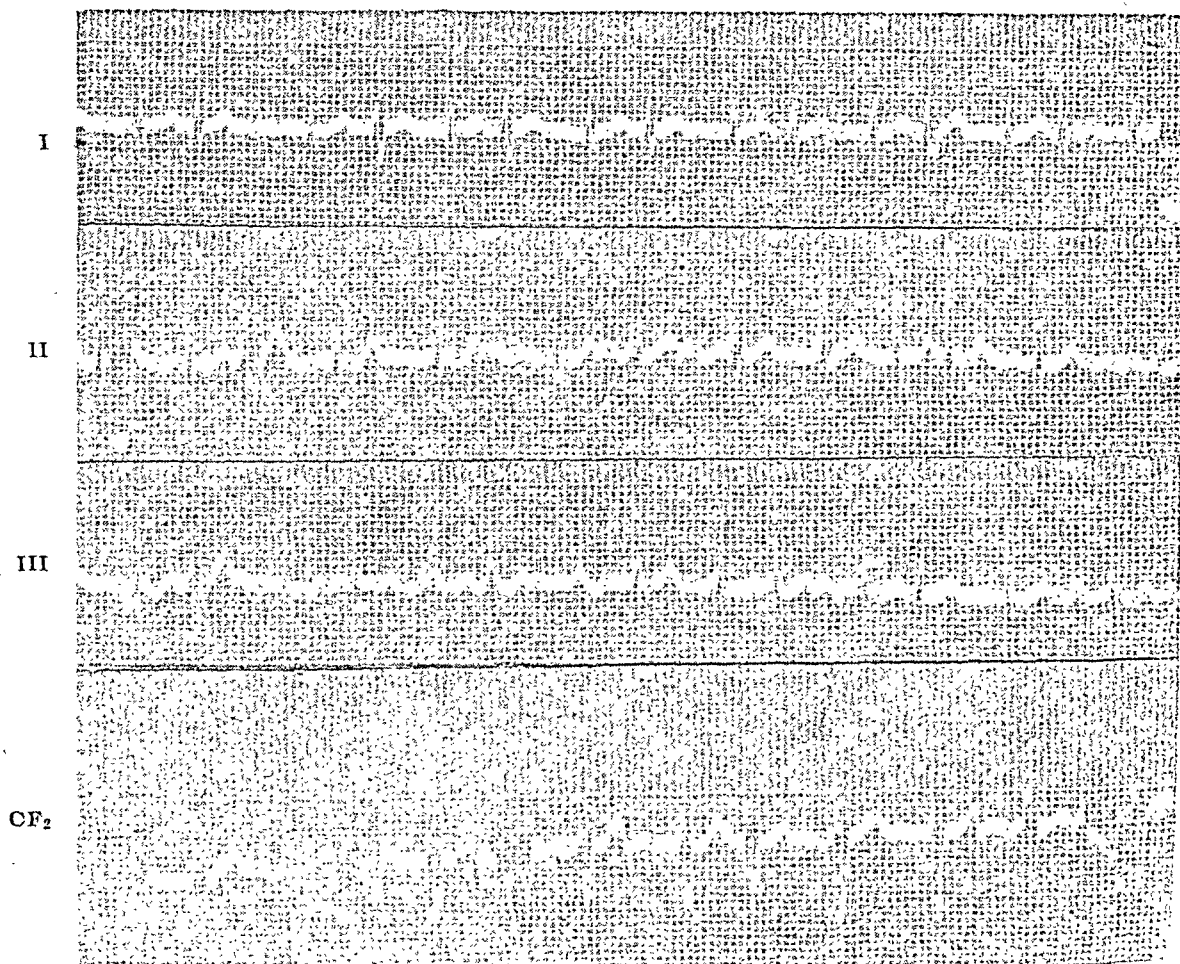


Fig. 2.—Leads I, II, III, and CF_2 taken one and one-half hours after the administration of 3 grains of quinidine sulfate. The auricular fibrillation appears to be a little coarser than before; the ventricular rate is higher. Aberration is now frequent; and when it is present the delay in the right bundle branch varies from slight to probable complete blockage.

short cycles follow cycles of average length, aberration of the QRS complexes is seen. All degrees of aberration are observable. In Lead I, the least change is shown by a slight increase in the amplitude of the R and S waves; but widening of the QRS is not clearly demonstrable. When there is a little more aberration, the S wave widens, the R wave has nearly the height of the usual R wave, and the QRS complex is widened by about 0.01 second. Still more aberration

is shown by further widening of the S wave; and a final stage is seen when the S is very wide and the QRS complex has the typical right bundle branch block form. In Lead III the complex near the middle of the strip is about 0.11 second in duration; while the greatest degree of aberration is shown by a complex near the beginning of the strip, the duration of which is at least 0.12 second. The precordial leads confirm the interpretation of a deficit in right bundle branch conduction for these widened complexes.

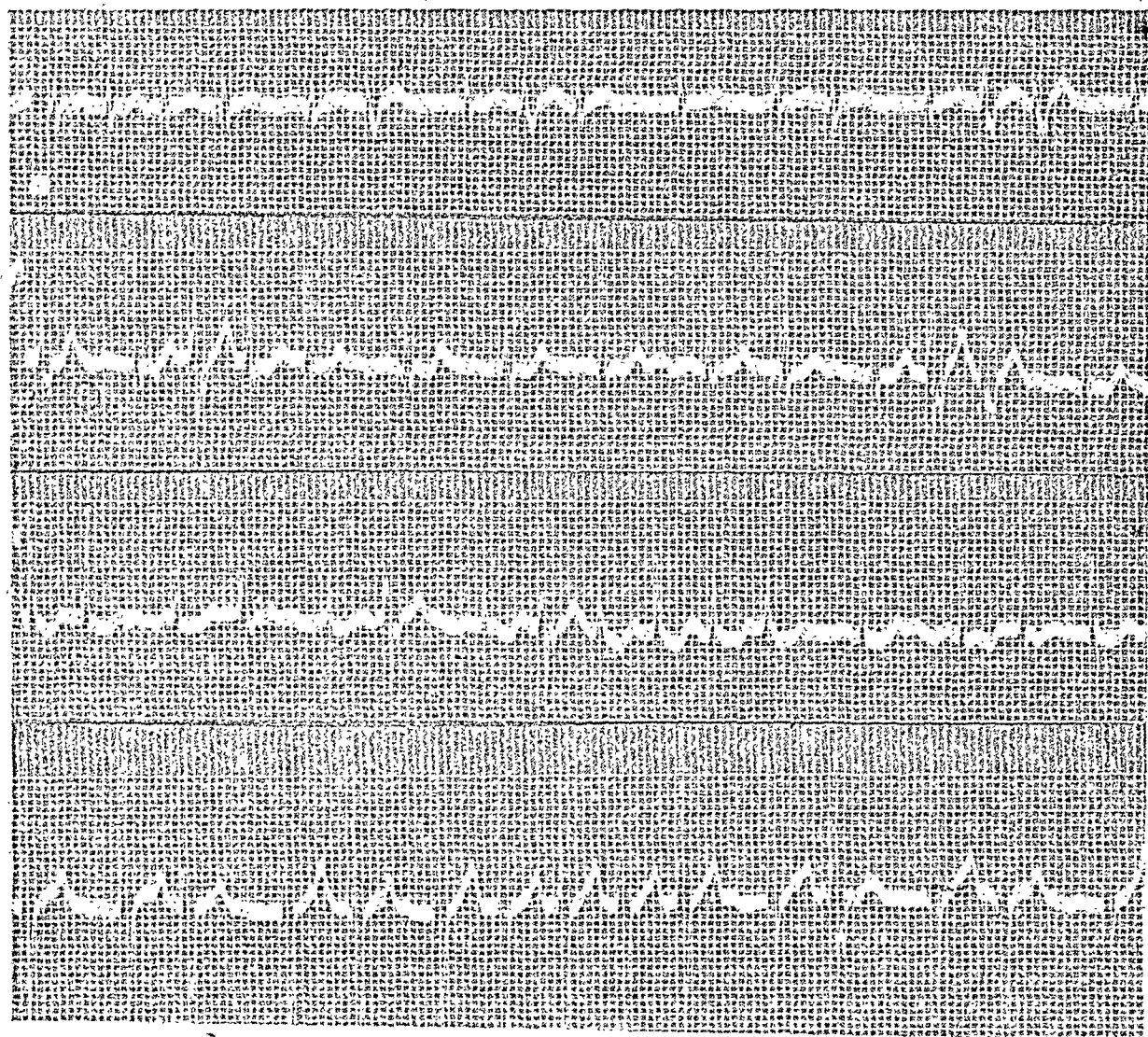


Fig. 3.—Leads I, II, III, and CF_4 taken two hours after Fig. 2.

At 1:00 P.M., the electrocardiogram differs from the earlier one in showing occasional pairs of aberrant complexes (Fig. 3). In only one place on the earlier electrocardiogram did a short cycle follow a markedly aberrant complex. This cycle was 0.31 second, and the QRS complex at its end was not aberrant. In the tracing of which Fig. 3 is a sample, widely aberrant complexes are often followed by short cycles and these are of the following durations, measured in hundredths of a second: 29, 23, 28, 27, 29, 24, and 25. Without exception, the beat terminating these cycles also shows great aberration when the cycle is

0.27 second or less. When the cycle is 0.28 second or longer, the beat ending it shows no aberration.

At 3:00 P.M., nearly two hours after the administration of an additional 6 grains of quinidine sulphate, the rate of the fibrillating auricles has become yet slower and the ventricular rate has increased (Fig. 4). At times, for periods as long as three seconds or more the ventricles are almost, but not quite, regular and the rate ranges from 192 to 196 per minute. In Lead I, a single, markedly aberrant complex is seen. Its width, however, is not over 0.10 second. After 0.29 second, this cycle is followed by a QRS complex which shows no aberration.

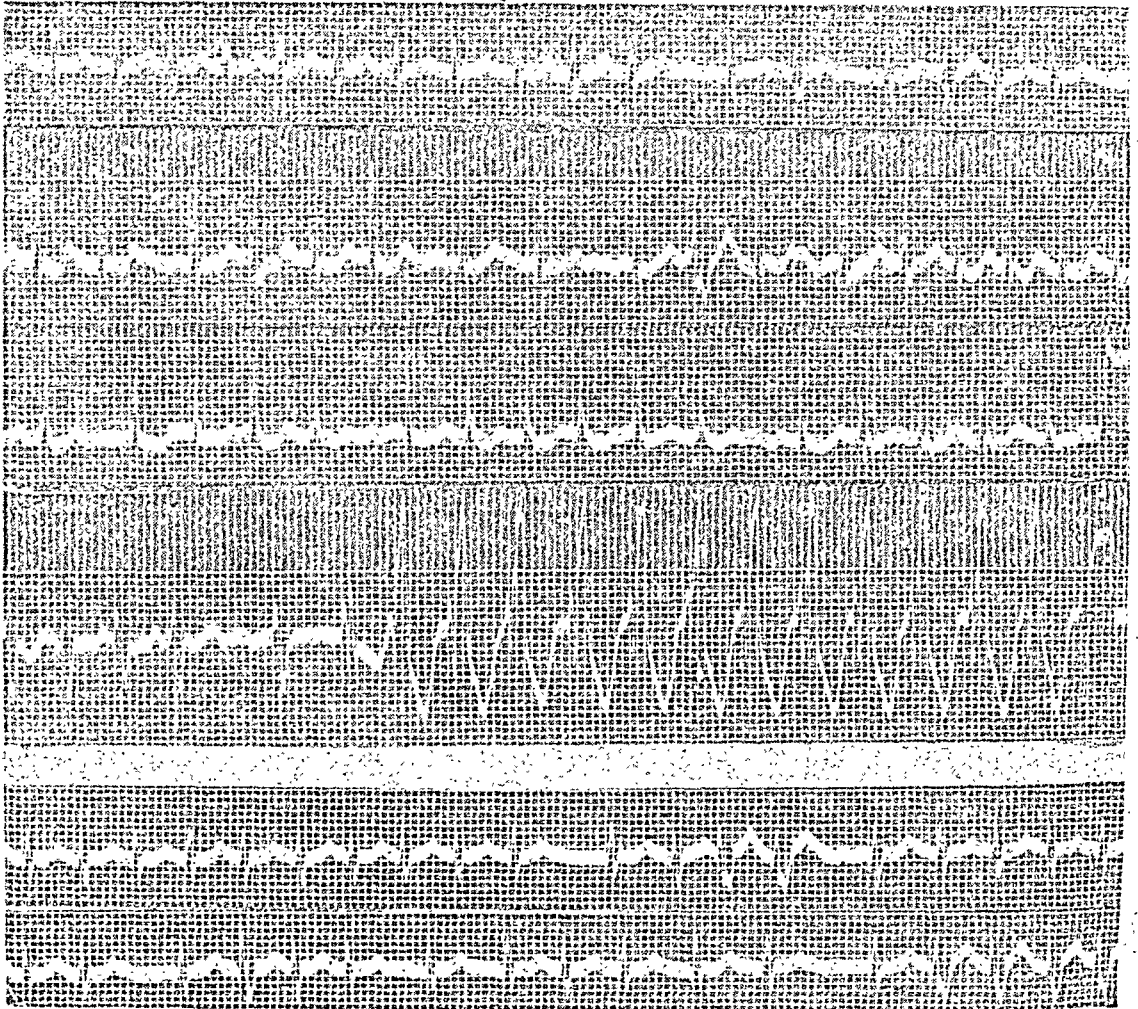


Fig. 4.—From above downward, Leads I, II, III, and CF_1 taken after the administration of 6 additional grains of quinidine. The two lower strips are Lead I from a slightly later electrocardiogram. A series of aberrant complexes in Lead CF_1 ends just as the standardizing current is sent in. In the last strip a longer series begins, which continued until the film was stopped. Note that the average rate during these series is no higher than the rate on other parts of the tracings, and that the same type of irregularity is present.

In Lead II, the same sequence is seen but the cycle following the wide QRS complex is about 0.33 second. In Lead III, near the end of the strip, a cycle of 0.73 second is followed by a 0.31 second cycle and the QRS complex is 0.12 second in width; the next cycle is 0.32 second, and QRS is wide, as is the next QRS.

complex which terminates a 0.34 second cycle. The next cycle is also short (0.34 to 0.35 second), but the QRS complex shows little aberration. In the precordial lead (CF_1), a series of twelve greatly aberrant complexes is seen. The series is ushered in when a very short cycle of 0.24 or 0.25 second follows a cycle of 0.36 second, which is terminated by a moderately aberrant QRS complex. During this period of what looks like ventricular paroxysmal tachycardia, the successive ventricular cycles, measured from the peak of each R wave (not R^1) to the next, are, in hundredths of a second: 30.5, 30.5, 31, 31.5, 30, 30, 31, 29.5, 31, 32, and 32.5; and the next cycle, ended by a narrow complex, is 31.5. Earlier on this same lead there was a period of rapid ventricular action with successive cycles, in hundredths of a second, of 33, 31, 33, 33.5, 30.5, 29.5, 30.5, 29.5, 30.5, 29.5, and 30.5. We here see the same slight irregularity and, toward the end, an even faster mean heart rate. *Yet there is no aberration.* Not counting the series of only three wide complexes, this electrocardiogram and a later one show five other series of wide complexes, and the rate and slight irregularity can always be duplicated on a nearby part of the electrocardiogram which shows no aberration whatever. The series of two or more wide complexes are always ushered in when a short cycle follows a long one or when a very short cycle follows a short one; and, with one exception, they come to an end when there is sudden slight or greater increase in cycle length. In the exceptional instance two wide complexes are separated by an interval of 0.28 second, the next cycle is 0.315 second and the complex is aberrant but not very wide; the following long cycle ends this short series. Another electrocardiogram taken a little later is like this one, except that the rate has gone up to about 200 per minute during the periods of more rapid ventricular action (Fig. 4, lowest strip).

In these electrocardiograms, therefore, we see all degrees of aberration resulting from various amounts of delay in right bundle branch (or "tract") conduction; and we see complexes which suggest complete right bundle branch block. All the complexes in the series of beats which look like ventricular paroxysmal tachycardia are wide and of bundle branch block form. We also see periods of equally rapid rhythm without wide complexes. How are we to account for these findings?

INTERPRETATION

It has been supposed that aberration of a single complex, following an auricular premature beat, occurs when the supraventricular impulse finds one bundle branch or a main strand of Purkinje fibers effectively refractory upon its arrival at the level of the bundle branch.¹ In another paper, it is pointed out that in the normal heart the delay or blocking of the impulse may possibly occur at a higher level,⁵ yet the explanation is presumably essentially correct. We have shown that the widening of the QRS complex in our case reached a limit at about 0.12 second and that this suggested complete right bundle branch block. The reason why the blocking persists if the period of rapid rhythm is ushered in by a wide complex, but not if the first complex is narrow, is probably simple. Once an impulse is blocked off from or within the right branch it first enters the left

ventricle. It then passes through the interventricular septum to the right ventricle, and is conducted backward up the right branch to the main bundle where it is blocked, since the main bundle is refractory at this time. We estimate that the time required by the impulse to go through the septum and back up the right branch is at least 0.07 second. If, then, after quinidine, another supraventricular impulse comes down 0.30 second after the one which was conducted aberrantly it reaches the right bundle (or a tract in the main bundle leading into the right bundle) after a rest period in that tissue of not over 0.23 second. This rest is not long enough to allow recovery from refractoriness and to permit the impulse to enter the right branch; therefore, this second impulse is also aberrant. As long as no slightly longer rest occurs in the *junctional tissues*, the right bundle branch block must persist and the electrocardiographic appearance is that of ventricular tachycardia. Once an impulse from above goes through the right branch, even though it is delayed, the cycles may then shorten to 0.28 second or less without aberration.

Aberration occurs when a short cycle follows a long one because the refractory period varies with cycle length. Hence, if a cycle is 0.52 second in this heart after quinidine (Fig. 4, beginning of Lead I, bottom strip), an impulse descending 0.33 second later is delayed but not blocked off from the right ventricle. An impulse following this 0.33 second cycle in 0.285 second experiences minimal aberration. Later in Lead I there is a cycle of 0.77 second. Hence, the refractory period is long, and an impulse descending 0.32 second later is prevented from entering the right ventricle by way of the right branch. It is evident that the *effective* refractory period, which is not necessarily the absolute refractory period but rather a degree of refractoriness which prevents passage of the impulse locally, is longer in the right branch or in some fiber bundle leading to that branch than it is elsewhere. In about 85 per cent of all patients whose electrocardiograms reveal aberration in the distribution through the ventricles of premature supraventricular impulses, it is the right ventricle which is activated late.⁵ Obviously, no reason can be given for this fact. It must depend upon some normal structural and/or physiologic peculiarity of the human junctional tissues.

For accuracy it must be noted that the interval between the ventricular beats is not a true measure of the rest interval in the A-V junctional tissues where the blocking occurs.^{1,5} It is probably for this reason that minor apparent discrepancies exist between expectation and fact in many cases of auricular fibrillation which reveal aberration of certain QRS complexes. These matters are discussed elsewhere in more detail.⁵

It is not unusual in auricular fibrillation to observe two successive complexes which are widened by aberration, as in this case. It is less common to encounter cases, such as this one, in which ventricular paroxysmal tachycardia is simulated.

SUMMARY AND CONCLUSIONS

The electrocardiogram of a patient with auricular fibrillation is discussed. After the administration of quinidine sulfate the atrial rate was slowed and

the ventricular rate was increased. Numerous aberrant QRS complexes were seen, occurring either singly or in groups of two, three, or more. At several places on the tracings, groups of from six to thirty-three wide, aberrant QRS complexes were seen. At other places, periods of equally rapid ventricular rhythm appeared, but the QRS complexes were narrow. Both when the complexes were wide and when they were narrow, the same slight irregularity in rhythm was found. Reasons are given for believing that the series of wide complexes are due to aberration in the conduction of the supraventricular impulses through the ventricles and that they do not represent ventricular paroxysmal tachycardia, which they closely resemble.

The probable mechanism is described whereby the aberration, once initiated, is maintained.

REFERENCES

1. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons, Ltd., p. 229.
2. Barker, P. S., Johnston, F. D., and Wilson, F. N.: The Effect of Quinidine Upon Sinus Tachycardia, Including the Production of Transient Bundle Branch Block, *AM. HEART J.* 25:760, 1943.
3. Miller, H.: Transitions Between Normal Intraventricular Conduction, Bundle Branch Block, and Ventricular Tachycardia, *AM. HEART J.* 19:364, 1940.
4. Wilson, F. N., Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *AM. HEART J.* 9:472, 1934.
5. Ashman, R., Byer, E., and Gouaux, J. L.: Atrioventricular Conduction in the Human Heart. II. Aberration of QRS Complexes in Auricular Premature Beats and Fibrillation, After Interpolated Ventricular Premature Beats, and in Supraventricular Paroxysmal Tachycardia. (In press.)

THE SUPERNORMAL PHASE OF RECOVERY OF CONDUCTION IN THE HUMAN HEART

I. MACK, M.D., R. LANGENDORF, M.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.

A SUPERNORMAL phase of recovery in excitable tissue was first described in nerve by Adrian and Lucas.¹⁻³ They found that during a critical period immediately following the passage of an impulse, the tissue was more excitable than usual. An impulse set up during this critical period was conducted faster than the previous impulse, or than an impulse set up earlier or later. Furthermore, a stimulus which would ordinarily be too weak to set up an impulse would be effective if applied during this period. When a region of partial block was present, an impulse which ordinarily would be stopped would pass the region of block if the stimulus were applied during this critical period. To this period of overswing of recovery of excitability and conductivity of the nerve, they applied the term supernormal phase. A similar phenomenon was observed⁴ in the turtle heart when the region between the auricles and ventricles was compressed. The phenomenon was more likely to be present when, in addition to compression (injury), there was also marked fatigue.⁵ Lewis and Master⁶ were unable to demonstrate a supernormal phase in the dog's heart. Hoff and Nahum⁷ demonstrated a supernormal phase in the cat's ventricle. However, their experiment showed a supernormal phase of recovery of excitability rather than of conductivity of the ventricular muscle.

In a large number of human cases of partial auriculoventricular block where the requisite injury and fatigue are present, cases are occasionally seen in which a supernormal phase of recovery of conduction seems to be present. There have been a number of reports^{8,10-18,21} of isolated cases which supposedly demonstrate this phenomenon. In this report we shall review the literature and differentiate those cases that convincingly show a supernormal phase from those in which some other mechanism appears to be acting. A hitherto unreported case which we consider demonstrates a supernormal phase of recovery will be included as well as a second case of apparent supernormal phase. This second case appears to be more readily explained on an entirely different basis.¹¹

ANALYSIS OF THE REPORTED CASES

The first instances of supposed supernormal phase of recovery to be reported in the human heart were described by Lewis and Master⁸ in 1924. However,

From the Cardiovascular Department, Michael Reese Hospital. Aided by the A. D. Nast Fund for Cardiovascular Research.

The department is supported by the Michael Reese Research Foundation.

Received for publication Jan. 28, 1947.

both cases were criticized by Wenckebach and Winterberg⁹ who explained the mechanism by interference with dissociation rather than a supernormal phase of recovery. Their first case of almost complete auriculoventricular block with sinus impulses being conducted only when the P wave fell in a critical period after the preceding QRS complex seems to be quite well explained by the supernormal phase of recovery. However, an idioventricular rhythm was present, so that dissociation with ventricular capture could also be used to explain the type of conduction seen. Their second case, however, is definitely not an example of the supernormal phase. It is simply a case of partial auriculoventricular block with the Wenckebach phenomenon, with nodal escape beats arising below the region of block so that the sinus impulses appearing immediately after a nodal beat, if not interfered with, were conducted with aberrant conduction.

Ashman and Herrmann's¹⁰ two cases which they believed to illustrate the supernormal phase of recovery can both be explained by other mechanisms. In their first case complete auriculoventricular block supervened whenever auricular slowing occurred, and impulses of sinus origin were again transmitted only when the P wave fell within a critical period (which they considered the supernormal phase) following the idioventricular beat. However, the coincidence of sinoauricular slowing and the intervention of complete auriculoventricular block may be explained by a spontaneous increase in vagus tone producing both effects. The authors did not accept this as an explanation since auricular acceleration did occur later after complete auriculoventricular block and ventricular standstill had been present for some time, yet without resumption of auriculoventricular conduction. However, during ventricular asystole, anoxia of the conducting tissues might conceivably have become so severe that the block was further intensified, in spite of the fact that vagus tone decreased, as indicated by auricular acceleration. Furthermore, with prolongation of cycle length, there is a prolongation of the refractory period of the conduction system.⁶ The appearance of idioventricular beats could then result in improved coronary flow and improved conductivity, particularly when associated with a decrease in vagus tone, as was evidenced by shortened P-P intervals. The second case is even less clear than the first and their proof that certain sinus impulses are conducted is not convincing. Both cases contain many idioventricular beats which may give rise to retrograde conduction. The effects of such retrograde conduction (the significance of which will be discussed later) are in no place evaluated; nor are the possible effects of blocked sinus impulses considered. A mechanism similar to the one that Wolferth¹¹ advanced for his case might well have been operating in both cases.

Wolferth¹¹ described one case of almost complete auriculoventricular block with occasional ventricular responses to sinus impulses. He did not think the supernormal phase of recovery played any part in this case and he attributed the phenomenon to one of two factors: (1) Prolongation of the rest period in the critical area of block prior to transmission by a mechanism to be discussed in more detail with our second case. (2) Transient improvement of the nutrition in the area of block due to ventricular systole and increased blood flow.

Luten and Pope¹² described a case of 3:1 block with ventricular premature systoles and impulses of sinus origin which were conducted whenever the P wave fell during a certain critical period after the R wave of either a conducted or of an idioventricular beat. They did not think this was due to a supernormal recovery phase of the auriculoventricular conduction system, but thought that it was due to some effect of a previous systole on the ventricular excitability. They excluded the auriculoventricular node because the supernormal recovery phase, or critical period as they call it, had a position in the ventricular cycle which was constant for systoles of the same length, but which, with systoles of different length (as occurred with changes in rate), came at correspondingly different intervals after the beginning of R. However, it is not justifiable to exclude auriculoventricular conduction because of these reasons. It is well known that the refractory period of the auriculoventricular node and common bundle is affected by the preceding cycle length.⁶ Furthermore, the interposition of ventricular systole even affects the rate of discharge of the sinus node. This may be seen in some cases of second degree or complete auriculoventricular block where a P-P interval bridging a QRS complex is shorter than a P-P interval which does not include a QRS complex. For these reasons we feel that Luten and Pope's case is an example illustrating the supernormal recovery phase.

Pareja¹³ reported a case of partial auriculoventricular block in which he assumed the supernormal phase of recovery to be present. However, because of the shortness of the strip reproduced, it is impossible to be sure that some other mechanism is not acting.

Jervell¹⁴ reported a case of partial auriculoventricular block where the sinus impulses were conducted only when the P wave fell within a certain period following the ventricular complex. This case is doubtful, since in his first record the sudden appearance of complete auriculoventricular block could be a result of sudden increased vagus tone; this variability in vagus tone affecting auriculoventricular conductivity in an irregular fashion could simulate the supernormal phase of recovery. Furthermore, in his second record, the so-called conducted beats could be ventricular premature systoles. However, if a longer record had been presented and the same conditions had held, a supernormal phase would not be ruled out.

Scherf and Schott¹⁵ described two cases of partial auriculoventricular block in each of which auricular impulses occurring in a certain early phase of diastole were conducted faster than those which occurred later in diastole. Their cases resemble our first case, especially since their cases also have no beats of idioventricular or nodal origin, so that retrograde conduction does not complicate the picture. They illustrate the supernormal phase of recovery very well.

Kline, Conn, and Rosenbaum¹⁶ reported two cases which they believed illustrate the supernormal phase of recovery. Their first case resembles the first case of Ashman and Herrmann,¹⁰ and the same objections are pertinent. Their second case was one of complete auriculoventricular block with occasional retrograde P waves following some of the idioventricular beats. They believed that impulses arising in the auricles, although not conducted to the ventricles, produced in the depressed zone a supernormal phase which permitted retrograde

conduction. However, there is no conclusive evidence here for a supernormal phase of recovery, since the retrograde P waves appear whenever the refractory period in the auriculoventricular node produced by partial penetration of the sinus impulse has passed. If it is kept in mind that when the first half of P is being inscribed, or earlier, the sinus impulse has already reached the A-V node, it is apparent that every time a retrograde P does not appear, the sinus impulse is just passing through the auriculoventricular node or has just passed through, so that the retrograde impulse is blocked. This is, in effect, interference with dissociation between the forward conducted impulses of sinus origin and the impulses of idioventricular origin conducted in a retrograde fashion.

Froment, Masson, and Gonin¹⁷ reported two unusual cases of partial auriculoventricular block. Their first case demonstrates the supernormal phase of recovery. Their second case is similar to our second case. Moreover, it showed several instances where retrograde impulses from the idioventricular pacemaker actually reached the auricles and resulted in the inscription of a retrograde P wave. The explanation for the conduction of some of the sinus impulses may be the same as for our second case and for Wolferth's¹¹ case, and will be further discussed.

Korth¹⁸ presented a case of partial heart block in which impulses coming early in diastole were conducted faster than those coming later in diastole. This, although not described as such by the author, we consider to be due to a supernormal phase of recovery.

The supernormal phase of recovery may possibly account for the path-clearing effect ("Bahnung") of a nodal beat for subsequent auriculoventricular conduction as shown in animal experiments by von Skramlik.¹⁹ A human case supposedly illustrating this phenomenon, in which with periods of complete auriculoventricular block, the first nodal escape of each block period restored the A-V conduction and terminated a Morgagni-Adams-Stokes attack, has been reported by Kisch.²⁰

Segers and Van Dooren²¹ reported five cases of almost complete auriculoventricular block, four of which showed a slow idioventricular pacemaker with occasional "conducted beats." They believed the conduction occurred whenever a sinus impulse followed an impulse of idioventricular origin within a certain critical period, and called this period the supernormal phase. It would be impossible to rule out the supernormal phase of recovery, but Wolferth's type of explanation might also be used to explain the presence of the occasional conducted beats. However, for either explanation, retrograde conduction would have to be assumed, although no retrograde P waves were present. Furthermore, most of the idioventricular complexes had sinus P waves immediately preceding or immediately following them, and it would be unlikely that the retrograde impulse would reach the critical region of block before the sinus impulse in every case.

Since partial auriculoventricular block is not uncommon, and yet genuine instances of supernormal phase of recovery are seen to be extremely rare, it is not surprising that the supernormal phase of recovery of conductivity could not be found in the mammalian heart experimentally.

CASE REPORTS

CASE 1.—Our first case is that of a 56-year-old white man who was admitted to the Michael Reese Hospital with a myocardial infarct. The patient's course was complicated by acute urinary retention, necessitating a suprapubic cystotomy, and by pneumonitis. The only drugs administered were barbiturates orally, papaverine intramuscularly, and penicillin. No digitalis was given at any time. He was discharged approximately two and one-half months after admission. Early, the electrocardiogram showed the typical changes (Figs. 1 and 4) found in a posteroseptal infarct, with second degree auriculoventricular block. Later, there was some restitution of contour toward the normal, with only first degree auriculoventricular block.

In the electrocardiogram shown in Fig. 1 (Leads I, II, III, CF₂, and CF₄) partial auriculoventricular block is present with what on first inspection might appear to be the Wenckebach phenomenon. However, on closer examination it is seen that the P-R intervals do not gradually lengthen up to the point where the sinus impulse is blocked, and that the P-R intervals bear an unusual relation to the length of the corresponding R-P intervals. In the ordinary case of partial auriculoventricular block with the Wenckebach phenomenon, the P-R interval becomes longer as the R-P interval becomes shorter. Here, however, in many instances the P-R interval becomes shorter in spite of the fact that the corresponding R-P interval also becomes shorter. This is more clearly brought out in Table I, where the R-P intervals are listed in the order of increasing duration. It is seen that they readily fall into four groups. In Group 1, the calculated average R-P is 0.015 second and the average P-R corresponding is 0.575 second. In Group 2, although the average R-P interval is now 0.047 second and is longer

TABLE I. CASE 1. CLASSIFICATION INTO FOUR GROUPS OF THE P-R AND R-P INTERVALS IN THE FIRST FOUR LEADS IN FIG. 1. THE R-P INTERVALS HAVE BEEN LISTED IN THE ORDER OF INCREASING DURATION

GROUP	1		2		3		4	
	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)
	0	0.54	0.04	∞	0.12	0.68	0.68	0.50
	0	0.56	0.04	∞	0.12	0.69	0.70	0.48
	0	0.57	0.04	∞	0.12	0.70	0.70	0.48
	0	0.58	0.04	∞	0.13	0.68	0.70	0.48
	0	0.59	0.05	∞	0.13	0.69	0.71	0.48
	0.01	0.56	0.05	∞	0.13	0.69	0.71	0.48
	0.01	0.59	0.05	∞	0.13	0.71	0.71	0.50
	0.03	0.55	0.05	∞	0.14	0.68	0.72	0.48
	0.03	0.56	0.05	∞	0.15	0.66	0.72	0.49
	0.03	0.56	0.06	∞				
	0.03	0.61						
	0.04	0.64						
Average	0.015	0.575	0.047	∞	0.13	0.686	0.706	0.486

than it is in Group 1, the P-R interval is infinity (that is, the sinus impulses are blocked). In Group 3, the average R-P measures 0.13 second and the average P-R interval corresponding to it, 0.686 second. Here, in spite of the fact that

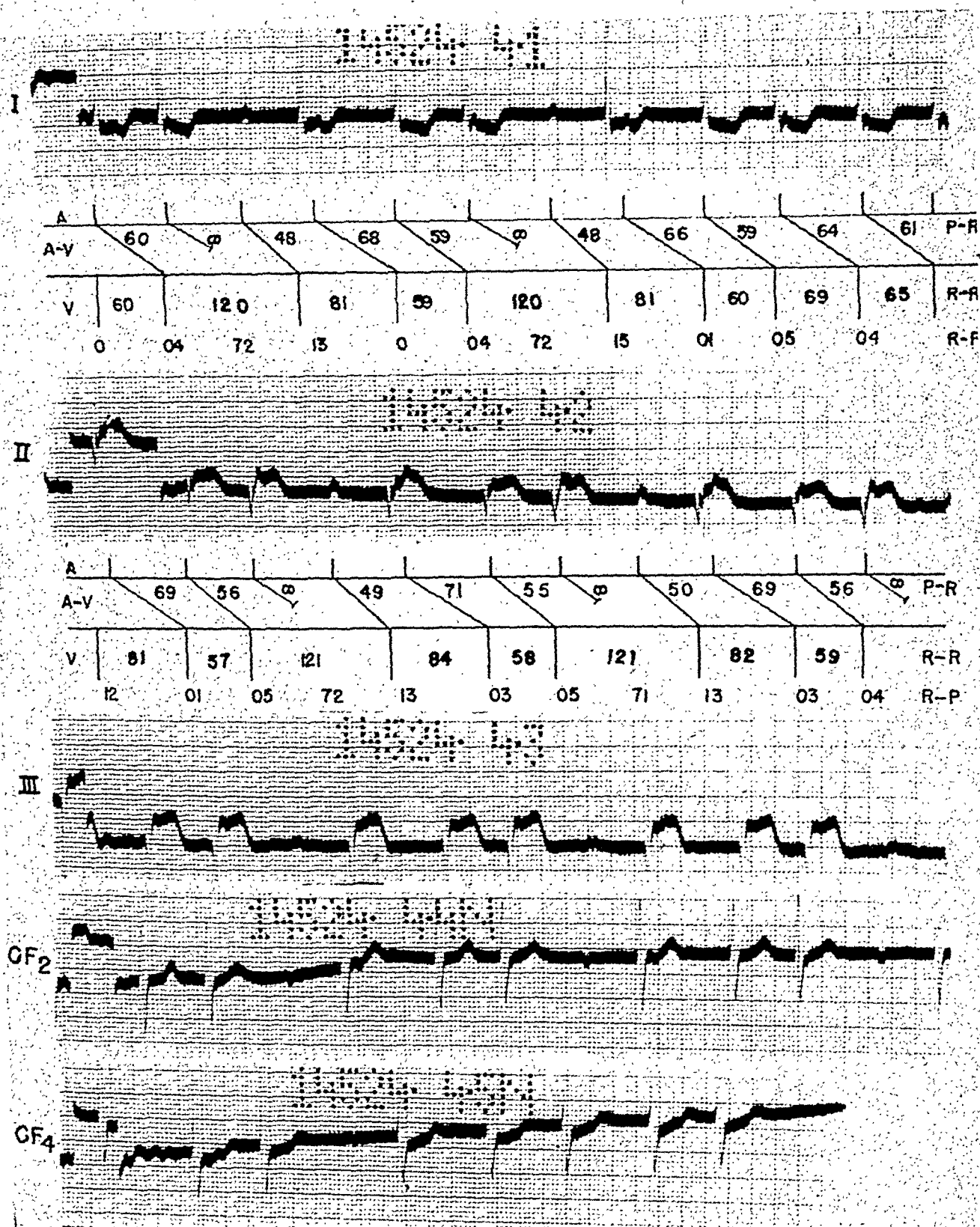


Fig. 1.—Case 1. Limb leads, and Leads CF₂ and CF₄ taken on Oct. 22, 1945. Diagrams demonstrating the conduction of impulses with values in hundredths of a second for the R-P, P-R, and R-R intervals are shown for Leads I and II. Discussed in text.

the average R-P is much longer than in Group 1, the average P-R is also much longer. This is extremely unusual in a case of partial auriculoventricular block. In Group 4 the average R-P measures 0.706 second and the average P-R, 0.486 second. The P-R intervals in this group are the shortest in the series. The most unusual feature is that of Group 1 where, in spite of a short R-P interval, the corresponding P-R is short also, and although not as short as in Group 4, yet

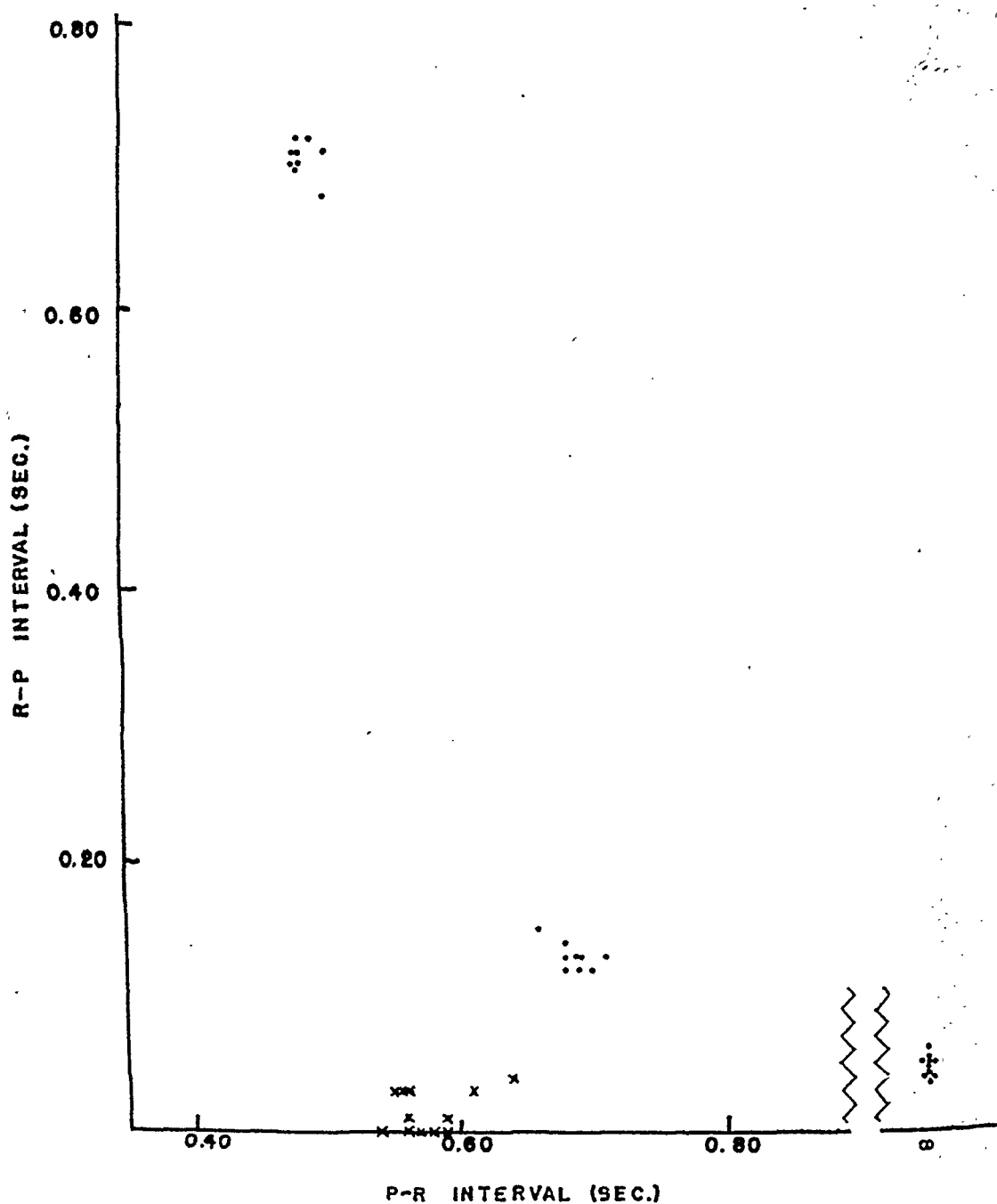


Fig. 2.—Case 1. The P-R and R-P intervals of the record in Fig. 1 are plotted, with the P-R along the abscissa and the R-P along the ordinate. Those beats conducted during the supernormal phase of recovery are indicated by crosses; other beats by dots. Discussed in text.

constantly shorter than in Groups 2 or 3. This phenomenon becomes easily explainable when one realizes that one is dealing with injured conducting tissue where the supernormal phase of recovery may be present. The reason why the sinus impulses are conducted with greater rapidity in Group 1 is that those sinus impulses are the ones that pass through the A-V node or common bundle within

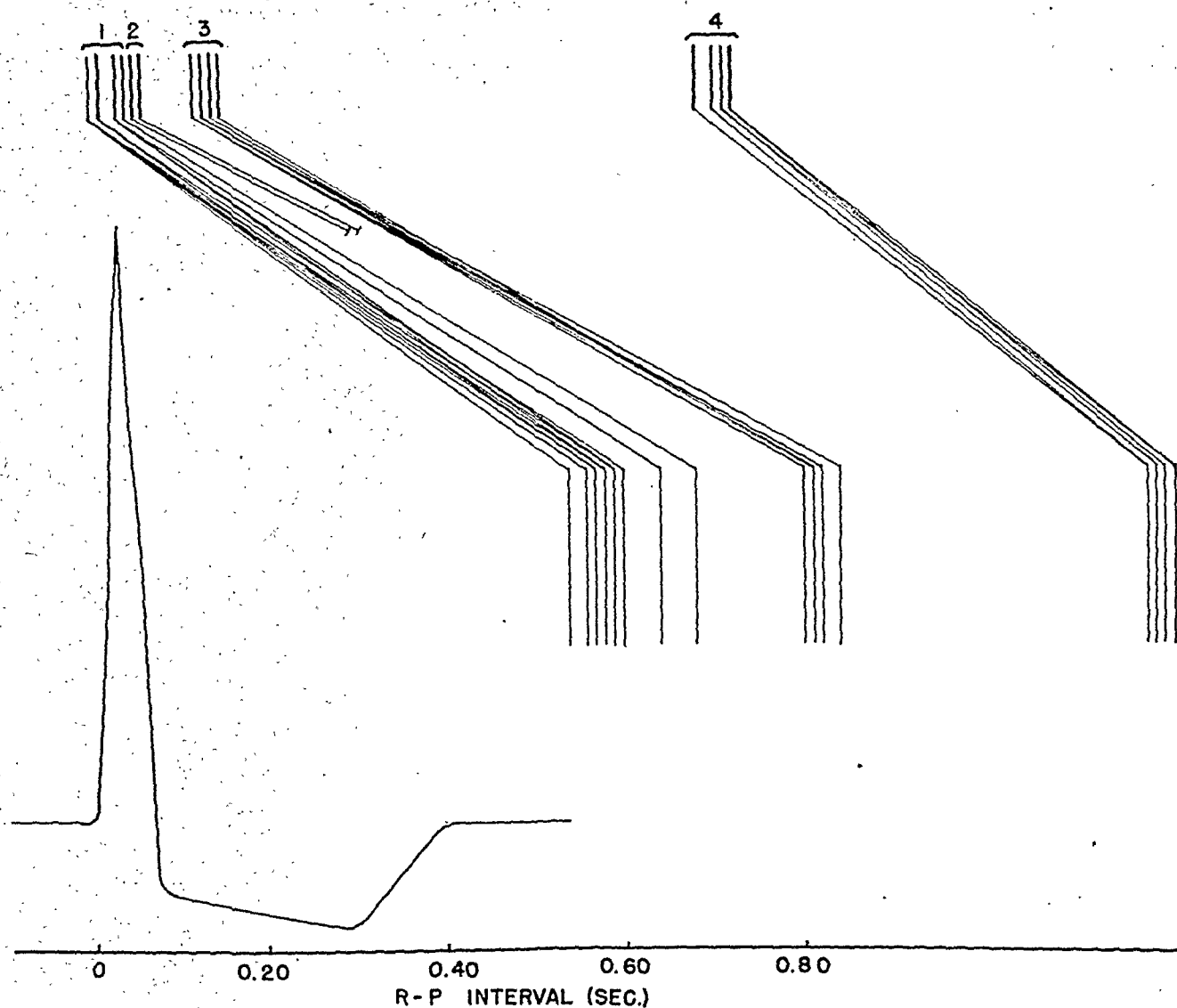


Fig. 3.—Case 1. Diagrammatic representation of the relation of the conducted and nonconducted sinus impulses to the preceding QRS complex. A division into four groups is indicated. In Group 1, the calculated average R-P is 0.015 second and the average corresponding P-R is 0.575 second; in Group 2, the average R-P is 0.047 second and P-R is infinity (blocked); in Group 3, the average R-P is 0.13 second and the average P-R is 0.686 second; in Group 4, the average R-P is 0.706 and the average P-R is 0.486 second. Where values for several beats are identical, the beats are indicated by a single line. This graph is to be compared with Table I.

a critical period of time when the conducting tissue is in the supernormal phase of recovery. The impulses in Group 2 fall just after the supernormal period and are not conducted. Impulses falling as late as those in Group 3 are conducted, but at a rate slower than those that fell within the supernormal period. Those in Group 4 are sinus impulses that follow a blocked sinus impulse, and because of the very long rest period that precedes them, are conducted faster even than

those that fell in the supernormal phase. Therefore, it should be noted that the term "supernormal" refers to the rate of recovery of conduction and not to absolute values of conduction speed. In this case the conduction during the supernormal phase is faster than expected, but not faster than normal. In the cases reported by Scherf and Schott¹⁵ the conduction during the supernormal phase was actually faster than that occurring after a long rest period, namely, after a blocked beat.

The relationship between R-P and P-R and the presence of the supernormal phase is shown in another way in Fig. 2. Here the duration of the R-P intervals is plotted along the ordinate and the P-R along the abscissa. It is seen that the beats exhibiting a supernormal phase (\times) fall in a group by themselves, and are outside of the recovery curve connecting the other beats. This is again shown in Fig. 3, the type of diagram utilized by Lewis and Master;⁸ the relation of the P waves to the preceding and succeeding QRS complexes is shown.

Fig. 4 shows an electrocardiogram taken two days *before* the one shown in Fig. 1. The same phenomenon may be seen. However, while the paradoxical shortening of the P-R intervals is seen in following any one series up to the dropping of a beat, when the entire group of P-R and R-P intervals are plotted on a graph (Fig. 5) the group of beats (\times) which were conducted during the supernormal phase do not fall into as distinct a group as those in Fig. 2. However, for any given R-P, the beat with the shortest P-R is always the one that was considered to fall into the supernormal period. This variation of actual location in the cardiac cycle of the supernormal phase is probably only apparent and is due to fluctuations in auriculoventricular conductivity which displace the supernormal period in the cardiac cycle. These fluctuations in auriculoventricular conductivity will also explain the apparent difference in position of the supernormal phase in the cycle in the records taken two days apart.

Hoff and Nahum²² believe that in the cat heart and the human heart the supernormal phase, when it occurs, falls on the same portion of the cycle as the U wave. However, as mentioned already, they were recording the supernormal phase of recovery of excitability of the ventricular musculature, and not of the conduction system. Furthermore, since a region of block is present, the apparent position of the supernormal phase in the cycle as derived from the R-P distance of the conducted beat will be determined by two factors: (1) Its actual position; and (2) the degree of conduction delay which will influence the specific time at which the impulse reaches the region where the supernormal phase becomes manifest.

There is an additional factor that affects auriculoventricular conductivity in cases of partial auriculoventricular block where there are variations in cycle length (for example, variations in ventricular rate). This is a phenomenon described by Lewis and Master⁶ when they found in the dog's heart that there was a definite change in the recovery curve of auriculoventricular conductivity with varying heart rates. At the higher ventricular rate (shorter cycle length) the recovery curve began earlier, so that a P-R interval corresponding to a R-P interval of given length was shorter for high rates than for low rates of beating;

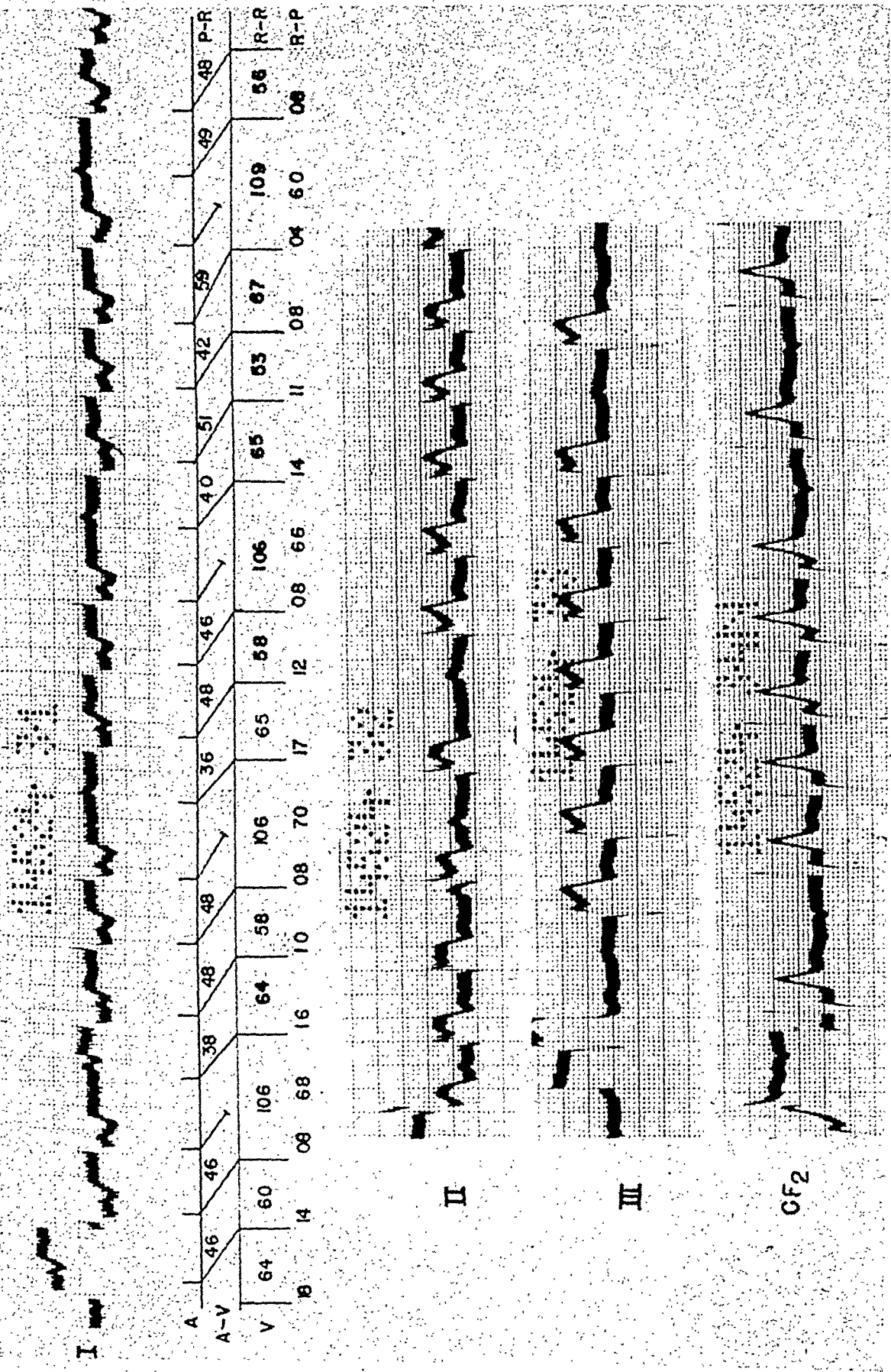


Fig. 4.—Case 1. Limb leads and Lead CF₂ taken Oct. 20, 1945. A diagram demonstrating the conduction of impulses with values in hundredths of a second for the R-P, P-R, and R-R intervals is shown for Lead I. Discussed in text.

this was found over the greater part of the recovery phase up to the time the curves crossed or ran together into a common plateau. Furthermore, they found that in passing from a slow to a faster rate of response it is the rule for the recovery curve to change after a single beat of the faster rhythm, so that the type

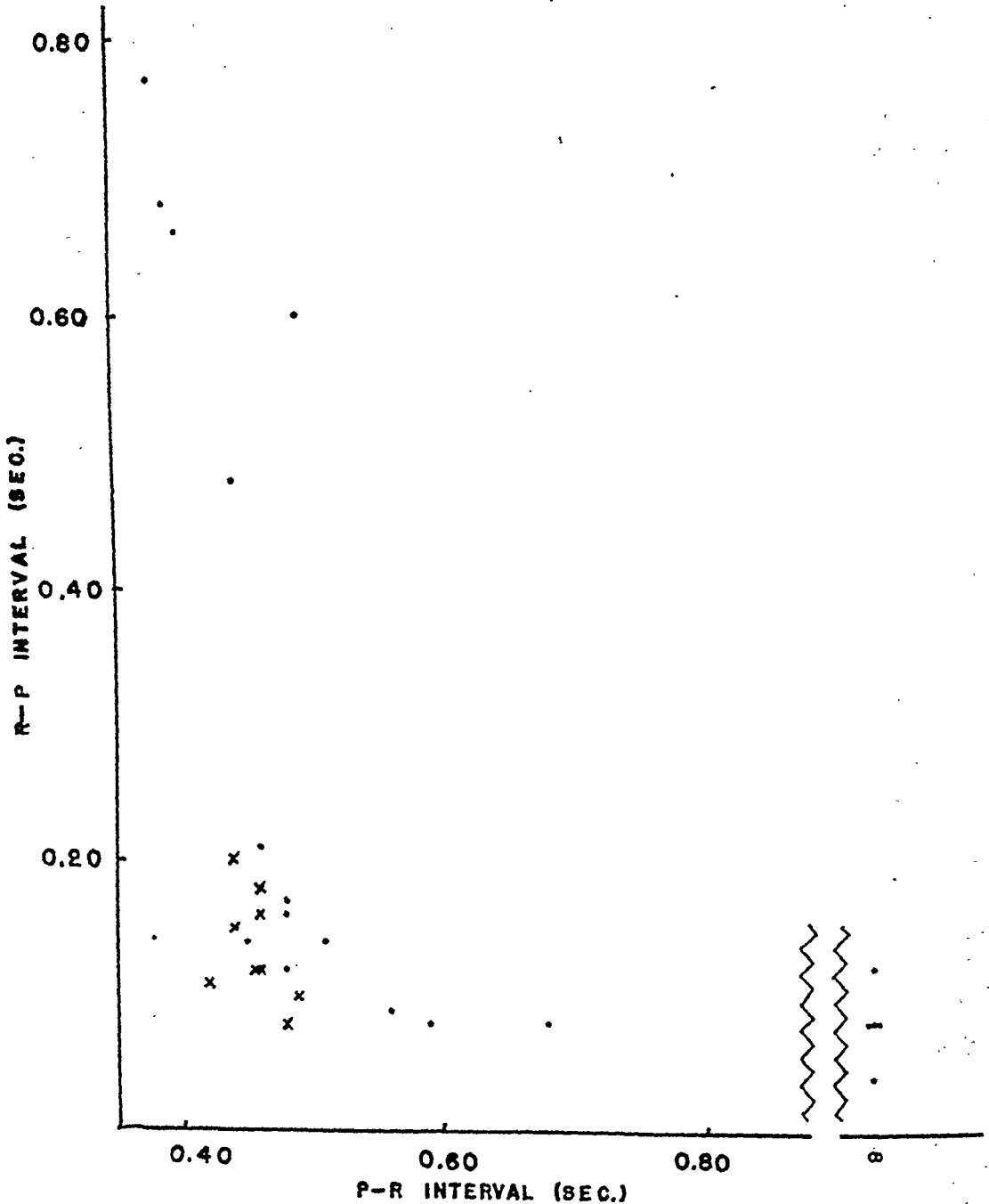


Fig. 5.—Case 1. The P-R and R-P intervals of the first two leads in the record in Fig. 4 are plotted with the P-R along the abscissa and the R-P along the ordinate. Those beats conducted during the supernormal phase of recovery are indicated by crosses; other beats by dots. For any given R-P the beat with the shortest P-R is the one that was observed in the record to fall in the supernormal phase of recovery. Discussed in text.

of recovery curve depends primarily on the length of the cycle which immediately precedes it. This may be restated: the refractory period of the conduction system will shorten when the cycle length shortens (rate increases). It is important to realize that the refractory period and recovery curves described by Lewis and Master are actually those of the tissues in which the variations of conduction are occurring and not of the excitability of the ventricular musculature.

This principle may be applied to a certain extent to our Case 1. Here it may be seen that the paradoxical shortening of the P-R intervals does often occur whenever the cycle length (R-R interval) shortens preceding the conducted beat. Since the R-R following a blocked beat is shorter than the R-R including the blocked beat, it is usually the second sinus impulse following one which is blocked that is conducted faster than expected. Thus, this mechanism may be acting in addition to the supernormal phase in our case. It is unlikely, however, that it alone is the factor responsible for the paradoxical shortening of the P-R intervals, *since there are several instances in the series where a shorter P-R interval appears even when the preceding cycle length is longer.* This may be seen usually where there are more than three consecutive conducted beats, as, for example, in the last group of P-R intervals in Leads I and CF₄ of Fig. 1, where the paradoxical shortening of P-R is still present even though the preceding cycle has become longer than the one preceding it. Moreover, it is doubtful that the effect of relatively slight variations in preceding cycle length on the refractory period of the conduction system would be so marked as to overcome the effect of marked shortening of the rest periods (R-P intervals) and give such a bizarre finding. In typical partial auriculoventricular block with the Wenckebach phenomenon, the P-R intervals, while becoming prolonged, it is true, to a *decreasing* extent before one is blocked, never actually get shorter than the preceding one. It is interesting to note that although Lewis and Master explained this feature of the Wenckebach phenomenon on the basis of changing recovery rates due to changes in cycle length, Decherd and Ruskin²³ have shown that it could be explained merely by the type of recovery curve present, the conduction time after complete recovery, and the auricular rate, without assuming a changing absolute or relative refractory period.

Our first case is thus seen to illustrate quite well the supernormal phase of recovery. Especially important is the absence of beats arising in nodal or ventricular pacemakers, so that the possibility of retrograde conduction does not complicate the picture.

CASE 2.—Our second case is that of a 65-year-old white woman with arteriosclerotic heart disease who was admitted to the hospital because of Morgagni-Adams-Stokes attacks.

An electrocardiogram (Fig. 6) revealed the presence of almost complete auriculoventricular block with occasional conducted beats. Comparison of the length of R-P intervals of the conducted beats with that of the blocked beats shows that we are not dealing with a case of dissociation with interference in the presence of a second degree auriculoventricular block. It was found that those

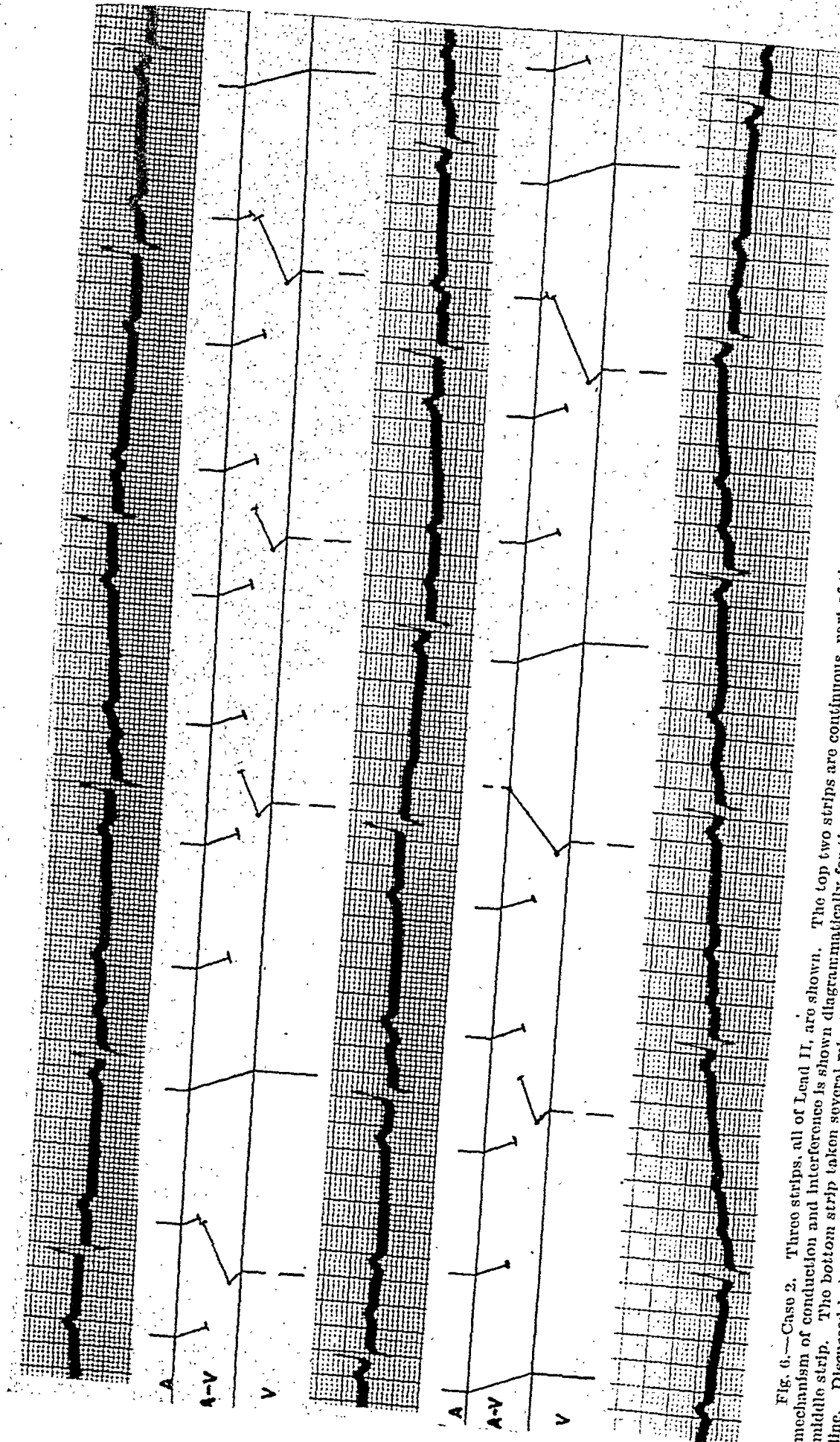


Fig. 6.—Case 2. Three strips, all of Lead II, are shown. The top two strips are continuous, part of the top strip being reproduced again in the middle strip. The middle strip. The bottom strip taken several minutes after the top two strips shows 2:1 conduction with a faster sinus rate. Nodal beats are indicated by a broken line. Discussed in text.

sinus impulses that were conducted always bore a definite relationship to the preceding QRS complex. One might then attempt to explain the conduction of some beats on the assumption that they fell during the supernormal phase of recovery of the greatly depressed auriculoventricular node or common bundle produced by a retrograde impulse of the nodal beat. This is the type of explanation utilized for several similar cases^{10,16} in the literature. Yet, if the conducted impulse were falling into a supernormal phase, the supernormal phase in this case would fall an unusually long time after the QRS complex, longer than in any case yet reported, and, moreover, after a blocked sinus impulse.

The P wave just preceding each conducted P wave bears a certain relationship to the nearest preceding nodal beat. It may be postulated that in the cases where the sinus impulses are blocked, these impulses are conducted to a certain region of the A-V junction where the block is especially marked, and it is in this region that the complete blocking occurs. Furthermore, each succeeding impulse penetrates to a certain extent into this region but usually does not get through. If, however, a nodal beat occurs with retrograde conduction, the retrograde impulse may reach the region of block sooner, traverse it, and interfere with (block) the sinus impulse above this region of severe block. Then, when the next sinus impulse reaches this region of severe block, this region having rested for a longer period of time than before, will now permit the sinus impulse to pass through. If, however, the nodal beat comes too soon after a sinus impulse has penetrated the region of marked block, then retrograde conduction from the nodal pacemaker would not penetrate up and interfere with the next oncoming sinus impulse. This explanation is that given by Wolferth¹¹ in his case. The mechanism is indicated by the diagrams in Fig. 6.

It will be noted that the third T wave in the second strip in Fig. 6, although produced by a fusion of P and T, is of much lower amplitude than would be expected from a fusion of a sinus P wave and an upright T wave of an amplitude seen elsewhere in the record. For this reason, it is quite probable that the P wave there recorded is not a sinus P wave, but is a retrograde P wave (inverted), or more likely yet, a fusion P wave (a P wave which is inscribed while the auricle is being invaded by an impulse from the sinus node and from below by a retrograde impulse from the A-V node). In the explanatory diagram shown just below this strip in the same figure, this P wave is represented as a broken line, and the line indicating retrograde conduction through the A-V node is shown entering the auricle. The slope of this line is represented as being steeper because the preceding P-R distance (R of the nodal beat) is long. Because the rate of retrograde conduction usually depends on the time elapsing between the discharge of the sinus node (even when the impulse only penetrates into the A-V node without reaching the ventricles) and the subsequent discharge of the A-V pacemaker, the duration of the R-P (retrograde) interval may be assumed to vary in an inverse fashion with the duration of the P (sinus)-R interval.

This mechanism was readily applied to a long record. During the course of taking this record, for a varying period of time, this patient developed relatively persistent 2:1 auriculoventricular block. This is seen in the bottom strip in Fig. 6. However, it is noted that the P-P distance in the bottom strip is shorter than

in the two upper strips. This speeding up of the sinoauricular pacemaker was probably associated with a decrease in vagus tone (or increase in sympathetic tone) which would also result in improved conductivity in the auriculoventricular node and common bundle.

While in Wolferth's case¹¹ there was no direct evidence of retrograde conduction, there is such evidence present in our case. However, even more clear-cut proof of retrograde conduction was found in the second of two cases reported by Froment, Masson, and Gonin.¹⁷ Their case could be considered to illustrate a supernormal phase of recovery. We believe, however, that the explanation of interference within or below the auricles between forward conduction of a preceding sinus impulse and retrograde conduction of a nodal impulse, which then facilitates the conduction of the next sinus impulse, is an alternative one. The presence of retrograde P waves tends to substantiate this explanation.

SUMMARY

1. An analysis of the reported cases of supernormal phase of recovery in the human heart is presented. In only five of these cases could the supernormal phase of recovery be considered present; in the others, different mechanisms appeared more likely.

2. A new case of partial auriculoventricular block is presented which demonstrates the supernormal phase of recovery. It was shown that the effect of cycle length on the refractory period was not sufficient to explain the paradoxical type of conduction exhibited and that a supernormal phase of recovery of the conducting tissue was responsible.

3. A second case of partial auriculoventricular block is presented which on first examination would seem to exhibit a supernormal phase of recovery. However, it was shown that auriculoventricular conduction occurred whenever a retrograde impulse reached the critical area of block prematurely, thus prolonging the succeeding rest period, and hence facilitating conduction of the next sinus impulse. This mechanism, reported by others, could be applied to some of the cases in the literature.

ADDENDUM

Since submitting our report, Segers and Denolin* reported a case of a 25-year-old man without evidence of heart disease, with marked sinus arrhythmia, and no A-B block, in which slowing of the sinus rate was associated with slight lengthening of the P-R intervals (0.20); speeding up of the sinus rate was associated with shortening of the P-R intervals (0.14). They attributed this to the supernormal phase of recovery. They did not believe that the findings could be due to changes in vagosympathetic tone because of the marked irregularity of the arrhythmia. However, this argument is not convincing because of the coincidence of the shorter P-R intervals with a faster sinus rate, making it quite likely that variations in vagosympathetic tone were responsible for the variations in A-V conduction. The possibility of a wandering pacemaker, as evidenced by changes in P-wave contour, could also be responsible for variations in duration of the P-R intervals. Another unusual characteristic of their case is the location of the supernormal phase of recovery in the cycle, and its long duration (0.40 to 0.70 second after the R wave).

*Segers, M., and Denolin, H.: *Etude de la Transmission Auriculo-Ventriculaire III. La Phase Supernormale de la Conduction*, Acta Cardiologica 1:279, 1946.

REFERENCES

1. Adrian, E. D., and Lucas, K.: On the Summation of Propagated Disturbances in Nerve and Muscle, *J. Physiol.* 44:68, 1912.
2. Adrian, E. D.: The Recovery Process of Excitable Tissue, *J. Physiol.* 54:1, 1920.
3. Adrian, E. D.: The Recovery Process of Excitable Tissues II, *J. Physiol.* 55:193, 1921.
4. Ashman, R.: Conductivity in Compressed Cardiac Muscle II, *Am. J. Physiol.* 74:140, 1925.
5. Ashman, R., and Wooley, E.: Combined Supernormal and Fatigue Phenomena in Compressed Cardiac Muscle of the Turtle, *Proc. Soc. Exper. Biol. & Med.* 23:159, 1925.
6. Lewis, T., and Master, A. M.: Observations Upon Conduction in the Mammalian Heart. A-V Conduction, *Heart* 12:209, 1925.
7. Hoff, H. E., and Nahum, L. H.: The Supernormal Period in the Mammalian Ventricle, *Am. J. Physiol.* 124:591, 1938.
8. Lewis, T., and Master, A. M.: Supernormal Recovery Phase, Illustrated by 2 Clinical Cases of Heart-Block, *Heart* 11:371, 1924.
9. Wenckebach, K. F., and Winterberg, H.: *Die Unregelmässige Herztätigkeit*, Leipzig, 1927, Wilhelm Engelmann, p. 336.
10. Ashman, R., and Herrmann, G. R.: A Supernormal Phase in Conduction and a Recovery Curve for the Human Junctional Tissues, *AM. HEART J.* 1:594, 1926.
11. Wolferth, C. C.: The So-Called Supernormal Recovery Phase of Conduction in Heart Muscle, *AM. HEART J.* 3:706, 1928.
12. Luten, D., and Pope, S.: Variations in Heart Block Sometimes Attributed to a Supernormal Recovery Phase, *AM. HEART J.* 5:750, 1930.
13. Pareja, J. M.: Période de Restauration Supernormale dans une Dissociation Auriculo-Ventriculaire Complète, *Arch. d. mal. du coeur.* 26:395, 1933.
14. Jervell, A.: Nachweis einer "supernormalen Reizbarkeitsphase" in einem Falle von partiellem Block, *Acta med. Scandinav. supp.* 59:626, 1934.
15. Scherf, D., and Schott, A.: The Supernormal Phase of Recovery in Man, *AM. HEART J.* 17:357, 1939.
16. Kline, E. M., Conn, J. W., and Rosenbaum, F. F.: Variations in A-V and V-A Conduction Dependent Upon the Time Relations of Auricular and Ventricular Systole. The Supernormal Phase, *AM. HEART J.* 17:524, 1939.
17. Froment, R., Masson, R., and Gonin, A.: Défaut de Subordination Ventriculaire dans les Blocks A-V partiels on frustes, *Arch. d. mal. du coeur.* 32:849, 1939.
18. Korth, C.: *Klinische Elektrokardiographie*, Berlin and Vienna, 1941, Urban & Schwarzenberg, p. 245.
19. Von Skramlik, E.: Die Bahnung der Erregung, *Arch. f. d. ges. Physiol.* 180:30, 1920.
20. Kisch, B.: Bahnung der Erregungsleitung im menschlichen Herzen, *Cardiologia* 9:326, 1945.
21. Segers, M., and Van Dooren, Fr.: La Dissociation A-V avec Captures Précoces du Ventricle. Etude de la Phase Supernormale de la Conduction, *Acta Cardiologica* 1:111, 1946.
22. Nahum, L. H., and Hoff, H. E.: The Interpretation of the U Wave of the Electrocardiogram, *AM. HEART J.* 17:585, 1939.
23. Decherd, G. M., and Ruskin, A.: The Mechanism of the Wenckebach Type of A-V Block, *Brit. Heart J.* 8:6, 1946.

THE ELECTROCARDIOGRAM IN NEUROCIRCULATORY ASTHENIA, ANXIETY NEUROSIS, OR EFFORT SYNDROME

PAUL D. WHITE, M.D., MANDEL E. COHEN, M.D., AND
WILLIAM P. CHAPMAN, M.D.
BOSTON, MASS.

SOME uncertainty has existed concerning the normality of the electrocardiogram in neurocirculatory asthenia because of occasional reports of unusual findings mingled with the general failure to discover any specific electrocardiographic pattern.

Lewis¹⁰ during the first World War found essentially normal electrocardiograms in cases of effort syndrome or neurocirculatory asthenia without characteristic pattern. In 1934 Craig and White³ reported an analysis of the electrocardiograms of thirty-five cases of "pure neurocirculatory asthenia"; in fifteen there was sinoauricular tachycardia (rate 110 to 160 per minute), in eight the T waves were diphasic in Lead II and inverted in Lead III, in six there was slight left axis deviation dependent on obesity, in five slight right axis deviation, and in one bigeminy due to auricular premature beats cleared by exercise. The next year (1935) Graybiel and White⁴ reported the discovery of inverted T waves in Leads II and III in seven cases (three men, four women) of neurocirculatory asthenia with no evidence of heart disease. Later, White and associates¹² concluded that such findings were dependent in major part on a vertical position of the heart and were generally corrected by a change to a supine body position, although in some cases sympathetic overstimulation, as by alarm or by the actual injection of adrenalin, could also markedly lower or even invert the T waves in Lead II, findings concurred in by other investigators. These changes can be produced whether or not there is neurocirculatory asthenia, though some cases with neurocirculatory asthenia do possess a slender body build and are easily affected by fright. Battro and Cobo¹ found slight elevation of S-T segments in some cases of neurocirculatory asthenia but this is a common finding in normal subjects. Hyperventilation has been stated by Thompson¹¹ and by others to depress the S-T segment and to lower or even invert the T waves in any or in all leads. Master⁹ and others have reported the frequent occurrence of right axis deviation in neurocirculatory asthenia apparently related to body

The work described in this paper was done under a contract between the Office of Scientific Research and Development and the Massachusetts General Hospital, which was recommended by the Committee on Medical Research.

From the Clinics of Medicine and Psychiatry and the Cardiac Research Laboratory of the Massachusetts General Hospital and the Departments of Medicine and Diseases of the Nervous System of the Harvard Medical School.

Received for publication Nov. 26, 1946.

build, but Master confined his observations to the "slender or asthenic type of individual with a low diaphragm and small heart." Finally, prolongation of the P-R interval has been noted in some few cases, as by Logue, Hanson, and Knight.⁸

A detailed study of soldiers with neurocirculatory asthenia by Cohen, Cobb, White and their colleagues² during World War II presented the opportunity to analyze their electrocardiograms in detail. The present paper summarizes the data secured in the analysis of the tracings of fifty male soldiers with neurocirculatory asthenia and fifty civilians, men and women, diagnosed as having anxiety neurosis and neurocirculatory asthenia in the psychiatric and medical clinics of a civilian hospital, a total of 100 young persons with this condition.

FINDINGS

Rhythm.—Normal rhythm was found in all cases, with a moderate amount of sinus arrhythmia in eleven.

Rate.—In the majority of cases (fifty-one) the heart rate was in the range of 70 up to 90; seven had rates below 70; twenty-two, from 90 to 100; and twenty, 100 or more beats per minute. This range of rate is somewhat higher than that customarily found in normal young adults unaccustomed to electrocardiography; for example, in the series of 1,000 healthy young aviators studied by Graybiel and his associates⁶ the range of heart rate was from 38 to 110, with the mean at 63.8, and over 100 beats per minute in only three cases.

P Wave.—The auricular complexes were within normal limits in all cases, although very small in three and diphasic in Lead III in one case.

P-R Interval.—The P-R interval measured 0.12 to 0.18 second in eighty-six cases, 0.11 second in one, 0.18 to 0.20 second, inclusive, in eleven, and over 0.20 second in two cases (0.22 and 0.24, respectively). It is probable that some chronic abnormality of auriculoventricular conduction existed in these two cases although there was no other evidence of heart disease. Nor was there any sign of active rheumatism.

QRS Wave.—The QRS complexes were within normal limits in shape, amplitude, and duration in all cases. Small Q deflections were found in Lead I in three patients and in Lead II in nine. Moderate Q deflections were present in Lead II in one case and in Lead III in ten. The duration of the QRS waves measured less than 0.10 second in eighty-six and just 0.10 second in fourteen. None showed intraventricular block.

Electrical Axis.—Measured according to Einthoven's triangle, the angle of the electrical axis ranged from 0° up to 90° in eighty-six cases, being 45° or more in sixty-three of these. In eleven subjects the angle was 90° or over, and it was less than 0° in only four. In only one case was the angle more minus than -30°. Thus, in nearly three-fourths of all the cases the angle was nearer the vertical than the horizontal.

Q-T Duration.—The duration of systole as measured by the time from the beginning of the QRS wave to the end of the T-wave equalled 0.30 to 0.35 second inclusive in seventy-eight cases, a perfectly normal duration for the heart rate which ranged mostly from 70 to 90 per minute, or a bit more or less. The duration was more than 0.35 second in twelve cases with the slowest pulse rates (50 to 55 in four cases and 60 to 70 per minute in six others); in no case was the measurement over 0.40 second. In seven patients the Q-T time was below 0.30 second but in none below 0.25 second; the shorter systoles were found, as was to be expected, in persons with faster heart rates, 100 or more per minute in all, with the fastest rate, 115 per minute, in the case with the shortest systole (0.25 second).

S-T Segment.—The S-T segments were flat in the limb leads in sixty-seven cases, slightly elevated in twenty-six (not over 0.5 mm. in Lead I or over 1 mm. in Leads II and III), moderately elevated in three (1.5 mm. in Lead III in one, 2.0 mm. in Lead III in one, and 2.0 mm. in Leads II and III in one), and slightly depressed in four cases (0.5 mm. or less in Lead II and in one case 1 mm. in Lead III). In Lead IV it was common, as it is normally, to find an elevation of 1 mm.; in one case there was an elevation of 2 mm. and in one other of 2.5 mm.; in no case where Lead IV was taken was its S-T segment depressed.

T Wave.—The T waves were upright in Lead I in every case, averaging 1.5 to 2.0 mm.; in seven cases the T waves were only 0.5 mm. high (or less) in this lead. In Lead II the T waves were upright in all cases except three, being flat in two of these and inverted (−1.5 mm.) in one; in these three exceptions the heart tended toward the vertical in position (axis angle 60° to 90°) and the first two may have their explanation therein, but the third with clearly negative T waves showed also negative T waves in precordial Leads CF₂, CF₄, CF₅, and CF₆ (−3.5 mm. in CF₄ and −3.0 mm. in CF₅) which strongly suggests some type of coincidental myocardial or pericardial involvement in that 20-year-old soldier. In Lead III the T waves were upright in thirty-eight cases, level in thirty-six more, diphasic in two, and inverted in twenty-four. Of the sixty cases in which Lead IV was recorded, fifty-seven showed upright T waves, two slight late notching, and one, referred to previously, distinct inversion not only of T₄ but of the T waves in the precordial leads from Positions 3 to 6, inclusive.

Precordial Leads.—A routine Lead IV was taken in sixty of the 100 cases and was clearly normal in fifty-seven. The QRS waves were an average normal in all sixty cases. In two cases the T waves were flat with slight late notching, the cause of which was not evident; there was no indication of heart disease; both had axis angles of 60°. The one case with clearly abnormal T waves in multiple precordial leads has been referred to previously.

Special Studies.—The effect of body position and of respiration was tested in six cases, little change in the electrocardiogram resulting except for slight axis deviation associated with change in heart position similar to changes described during respiration in healthy subjects. Strenuous exercise gave tachy-

cardia and lower T waves in the two cases so tested. Twelve cases subjected to the Master two-step test showed no changes in the electrocardiogram save for an increase in heart rate. In three cases hyperventilation led to an increase in heart rate in all three, no change in T waves in one, slight elevation of T_2 in one, and slight lowering of T_1 and T_3 in the other. The alarm reaction (by revolver shot), tested in Lead II, caused an increase in heart rate in four cases, no change in T waves in two cases, slight lowering of T waves in one case, and inversion of T_2 in the fourth case, similar to findings in healthy subjects.

DISCUSSION

A review of the literature, our own clinical experience during the past twenty-five years, and the present detailed analysis of 100 cases indicate the nonexistence of any characteristic pattern or pathognomonic evidence of neurocirculatory asthenia in the electrocardiogram. The variations from the average normal resting tracing can and should be attributed to unusual position of the heart (as a rule, extreme verticality), to the effect of exercise, excitement (alarm, for example), possibly overventilation, and, in very rare cases, quite probably to otherwise nonevident slight pathologic conditions. From these data it seems unlikely that simple emotion alone, such as "anxiety," leads to electrocardiographic changes as suggested by Loftus, Gold, and Diethelm.⁷ All 100 of our cases were examples of clinically diagnosable anxiety neurosis, and yet their electrocardiograms differed in no obvious way from those of healthy individuals. Prolongation of the P-R interval which has been noted in a few cases of neurocirculatory asthenia is to be ascribed to either an extreme normal variation or to coincidental heart disease, probably rheumatic (acute or chronic), not otherwise manifested, and is not to be attributed to the neurocirculatory asthenia itself. Thus, our two cases with prolonged P-R intervals very likely had suffered at some time in the past from some process that had slightly scarred their auriculo-ventricular conduction tracts, and our one case with persistently abnormal T waves in Leads II and III and precordial Leads CF_3 to CF_6 inclusive very probably had some unrecognizable type of myocardial or pericardial involvement. All 100 cases were carefully selected as characteristic instances of neurocirculatory asthenia in youth without clinical evidence of heart disease.

Had we found an appreciable number of clearly abnormal electrocardiograms in this series, would we have attributed the abnormalities to this condition itself? In all probability we would have done so unless the cases themselves had shown other definite causes for the abnormality. The very few unusual findings in this group were comparable both in type and extent to those which have been reported in the study of 1,000 healthy subjects.⁶

SUMMARY AND CONCLUSION

An analysis of the electrocardiograms of 100 cases of neurocirculatory asthenia, half soldiers and half civilians, has revealed no characteristic pattern. The few variations from the average normal record are those usually encountered in a group of healthy young men, and either are associated with well-known

factors such as body build, pulse rate, and posture, or are the effect of past illness.

One may, therefore, conclude that the electrocardiogram is normal in neurocirculatory asthenia.

REFERENCES

1. Battro, A., and Lavallo Cobo, J.: Modificaciones electrocardiográficas observadas en la astenia neuro-circulatoria, *Rev. argent. de cardiología*. 3:215, 1936.
2. Cohen, M. E., Johnson, R. E., Chapman, W. P., Badal, D. W., Cobb, S., and White, P. D.: A Study of Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome. Final Report to the Committee on Medical Research of the Office of Scientific Research and Development. Contract O.E.M.: c.m.r. No. 157, pp. 135, 1946.
3. Craig, H. R., and White, P. D.: Etiology and Symptoms of Neurocirculatory Asthenia. Analysis of One Hundred Cases, With Comments on Prognosis and Treatment, *Arch. Int. Med.* 53: 633, 1934.
4. Graybiel, A., and White, P. D.: Inversion of the T-Wave in Leads I or II of the Electrocardiogram in Young Individuals With Neurocirculatory Asthenia With Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, *AM. HEART J.* 10:345, 1935.
5. Graybiel, A., and White, P. D.: *Electrocardiography in Practice*, ed. 2, Philadelphia, 1946, W. B. Saunders Company.
6. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, *AM. HEART J.* 27: 524, 1944.
7. Loftus, T. A., Gold, H., and Diethelm, O.: Cardiac Changes in the Presence of Intense Emotion, *Am. J. Psychiat.* 101: 697, 1945.
8. Logue, R. B., Hanson, J. F., and Knight, W. A.: Electrocardiographic Studies in Neurocirculatory Asthenia, *AM. HEART J.* 28: 574, 1944.
9. Master, A. M.: Effort Syndrome or Neurocirculatory Asthenia in the Navy, *U. S. Nav. M. Bull.* 41:666, 1943.
10. Lewis, T.: Medical Research Committee: Report Upon Soldiers Returned as Cases of "Disordered Action of the Heart" (DAH) or "Valvular Disease of the Heart" (VDH), London, 1917, His Majesty's Stationery Office.
11. Thompson, P.: The Electrocardiogram in the Hyperventilation Syndrome, *AM. HEART J.* 25:372, 1945.
12. White, P. D., Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart, *Brit. Heart J.* 3:233, 1941.

THE RELATIONS OF T_1 AND T_3

EMANUEL GOLDBERGER, M.D.*
NEW YORK, N. Y.

SEVERAL investigators¹⁻³ have recently pointed out that an upward T_1 which is less than T_3 in amplitude ($T_1 < T_3$) is frequently a sign of myocardial infarction. No adequate explanation for this interesting observation has appeared; furthermore, T_1 may be less than T_3 in a normal person.¹⁻³ However, when persons who show a $T_1 < T_3$ pattern are studied by means of unipolar leads, the explanation for this phenomenon becomes evident.

MATERIAL AND METHOD

The tracings of 500 patients were reviewed for this study. In all these cases, unipolar extremity leads and multiple unipolar precordial leads were taken in addition to the three standard leads. The unipolar extremity leads were taken with the author's method of obtaining "augmented" unipolar extremity leads.⁴ All the unipolar leads were taken with the author's modification of Wilson's indifferent electrode of zero potential.⁴ Unipolar extremity leads were taken from the left arm, the right arm, and left leg. Precordial leads were taken over the following points on the chest wall: V_1 , precordial electrode over fourth intercostal space to the right of the sternum; V_2 , over the fourth intercostal space just to the left of the sternum; V_3 , between V_2 and V_4 ; V_4 , over the fifth intercostal space on the left midclavicular line; V_5 , on the left anterior axillary line at the level of V_4 ; and V_6 , on the left midaxillary line at the level of V_4 .

In this series, twenty-five tracings showed a $T_1 < T_3$ pattern. Seventeen were from persons with normal hearts, or with right or left ventricular hypertrophy. Eight patients had anterior infarction.

RESULTS

General Remarks.—Leads I and III are related, regardless of what their actual patterns are because the potentials of the left arm take part in the formation of both these leads. Lead I equals left arm minus right arm, and Lead III equals left leg minus left arm. As a matter of fact, the relations between the patterns of the left arm lead and Leads I and III can be expressed mathematically as follows:

From the Medical Division, Montefiore Hospital, New York, Dr. Louis Leiter, Chief.
Received for publication Jan. 15, 1947.

*Work done under a fellowship of the Martha M. Hall Foundation for Research in Cardiovascular Diseases (at Montefiore Hospital).

$$\text{left arm} = \frac{I - III}{3}^5$$

The proof of this is as follows:⁵

The above equation can be rewritten,

$$\begin{aligned}\text{left arm} &= \frac{(LA - RA) - (LL - LA)}{3} \\ &= \frac{LA - RA - LL + LA}{3}\end{aligned}$$

Since $RA + LA + LL = 0$,^{4,5} $LA = -RA - LL$,

therefore,

$$\text{left arm} = \frac{LA + LA + LA}{3}$$

$$\text{left arm} = LA.$$

Thus, if in a tracing Lead I has a T wave 3 mm. tall, and Lead III has a T wave 6 mm. tall, the amplitude of T in the left arm lead of such a case is $\frac{3-6}{3}$ or -1. $T_{\text{left arm}}$ is therefore downward and 1 mm. deep.*

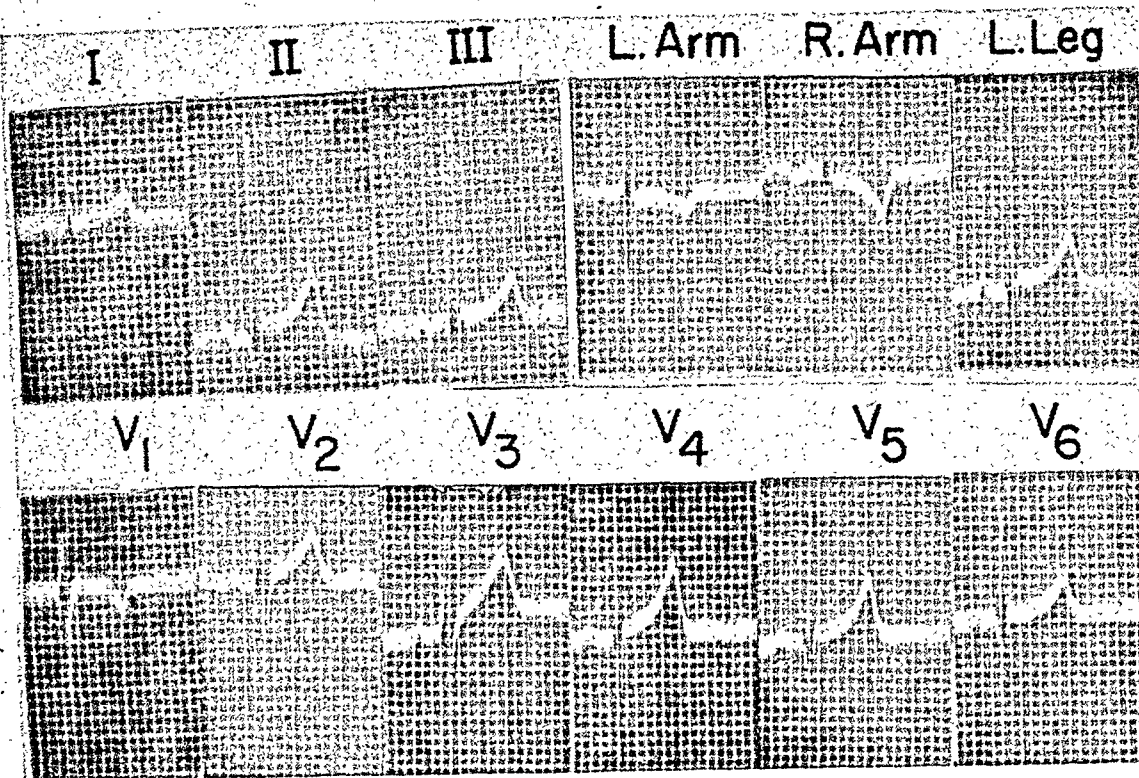
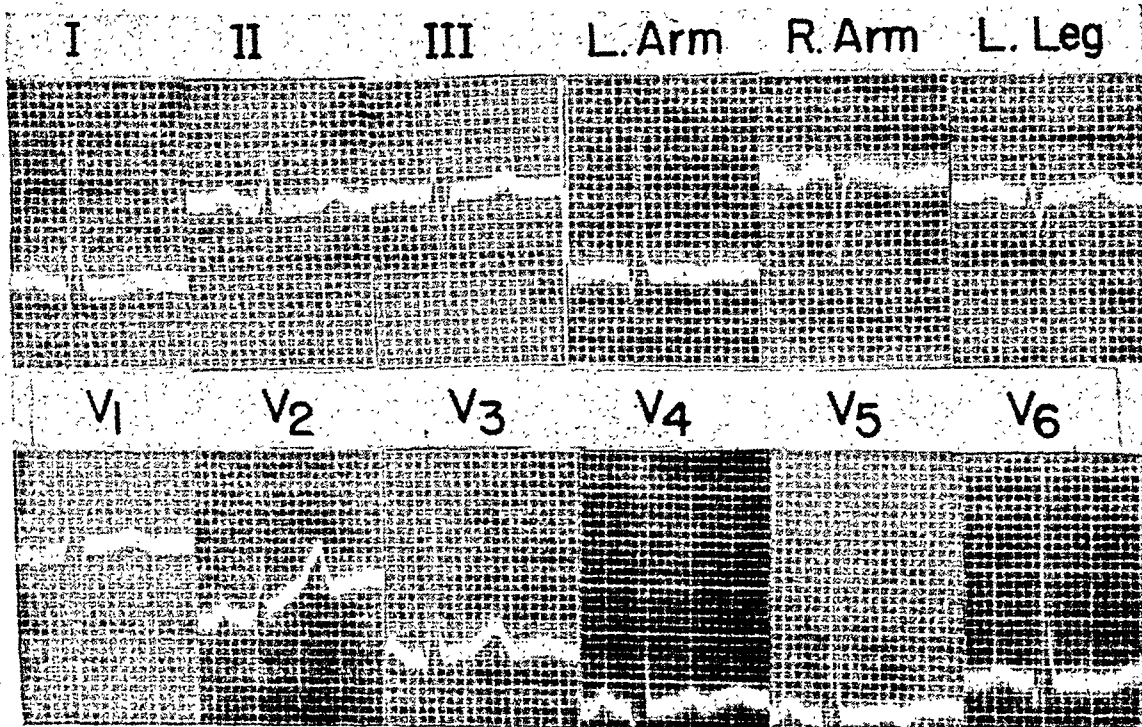
3

In other words, T_1 will be less than T_3 whenever $T_{\text{left arm}}$ is negative.

In all of our twenty-five cases with the $T_1 < T_3$ pattern, we found this to be so, regardless of whether the heart was normal or abnormal. Figs. 1, 2, and 3 show typical examples of this. Fig. 1 is the tracing of a 25-year-old normal man. Fig. 2 is the tracing of a 54-year-old woman with hypertensive cardiovascular disease. The downward T waves of precordial Leads V_5 and V_6 are typical of left ventricular strain. Although T_1 is upward, notice that the left arm lead resembles precordial Lead V_6 . Fig. 3 is the tracing of a 39-year-old man with anterior infarction. Precordial Leads V_2 , V_3 , and V_4 are typical of infarction although the standard leads appear normal. Although T_1 is upward, the left arm lead resembles Lead V_4 .

Criteria have been developed to determine whether a downward T in the left arm lead is normal or abnormal.^{7,9} This subject is too complex to be discussed here. However, it is important to note that all our cases with the $T_1 < T_3$ pattern showed the following: when the downward $T_{\text{left arm}}$ was normal or due to left ventricular strain, the precordial leads were normal or showed clear-cut evidence of left ventricular strain. When a downward $T_{\text{left arm}}$ was due to anterior infarction, the multiple precordial leads showed the patterns of infarction.

*The unipolar extremity leads illustrated in this paper are "augmented," and, therefore, their amplitudes are one and one-half times larger than the actual potentials at each of the extremities. Thus, in such an example as this, the left arm lead, as recorded, would show a downward T wave, 1.5 mm. deep.^{4,6}

Fig. 1.— $T_1 < T_3$ pattern in a normal person.Fig. 2.— $T_1 < T_3$ pattern in a case of left ventricular strain.

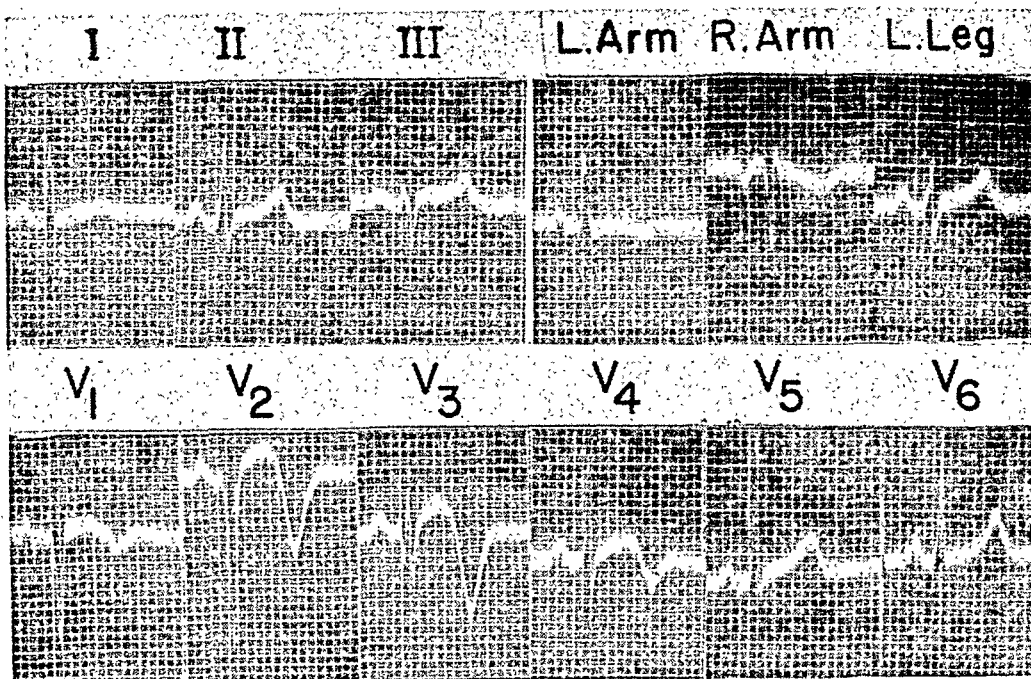


Fig. 3.— $T_1 < T_3$ pattern in a case of anterior infarction.

CONCLUSIONS

In the standard leads, T_1 may be less than T_3 in patients with anterior infarction. However, this pattern frequently occurs normally and in patients with left ventricular strain. It is due to the fact that the left arm, which takes part in the formation of both Leads I and III, shows a downward T wave in such cases.

The determination of whether the $T_1 < T_3$ pattern is normal or abnormal can be made by using multiple unipolar precordial leads. When the $T_1 < T_3$ pattern occurs normally, the multiple precordial leads are normal; when the pattern occurs after anterior infarction, the multiple precordial leads show typical patterns of anterior infarction.

REFERENCES

1. Ashman, Richard, and Hull, Edgar: *Essentials of Electrocardiography*, ed. 2, New York, 1941, The Macmillan Co.
2. Zwillinger, L.: Elektrokardiographische Zwischenstadien im Verlaufe der Coronarthrombose, *Ztschr. f. klin. Med.* 130:609, 1936.
3. Dressler, William: Myocardial Infarction Indicated by an Electrocardiographic Pattern in Which T_1 is Lower Than T_3 , *AM. HEART J.* 26:313, 1943.
4. Goldberger, Emanuel: A Simple Indifferent Electrocardiographic Electrode of Zero Potential, and A Technique of Obtaining Augmented, Unipolar, Extremity Leads, *AM. HEART J.* 23:483, 1942.
5. Wilson, F. N., Macleod, A. G., Johnston, F. D., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9:447, 1933.
6. Goldberger, Emanuel: The aVI, aVR, and aVF Leads, *AM. HEART J.* 24:378, 1942.
7. Goldberger, Emanuel: An Interpretation of Axis Deviation and Ventricular Hypertrophy, *AM. HEART J.* 28:621, 1944.
8. Goldberger, Emanuel, and Schwartz, S. P.: *Electrocardiograms in Chronic Pulmonary Disease*, *Am. Rev. Tuberc.* 53:34, 1946.
9. Goldberger, Emanuel: *Unipolar Lead Electrocardiography*, Philadelphia, 1947, Lea & Febiger.

CIRCULATORY EFFECTS OF THREE MODIFICATIONS OF THE VALSALVA EXPERIMENT

AN EXPERIMENTAL SURVEY

ROBERT F. RUSHMER, M.D.

LOS ANGELES, CALIF.

THIS report deals with a series of experiments designed to explore three modifications of the original Valsalva experiment as a possible means of testing the circulatory adaptation to gravitational forces in applicants for pilot training. Measurements have been made of the effect of these three straining procedures on the intragastric pressure, position of the diaphragm, size of the cardiac silhouette, arterial blood pressure, finger volume, and venous pressure in upper and lower extremities.

In 1740, Valsalva reported some observations made during forced expiratory effort against the closed glottis and, since that time, various modifications of the Valsalva maneuver have been advocated as tests for different aspects of cardiovascular efficiency in response to stress. The medical literature on this subject is extremely voluminous. Liedholm¹ presented a comprehensive review of the literature up to 1939, including a large portion of the reports appearing in the European literature. The majority of the opinions presented in this survey apparently agreed that the following represent the circulatory manifestations produced during the Valsalva experiments: the heart size, stroke volume, cardiac output, capillary flow, and venous return to the heart are reduced, while the heart rate, venous pressure, and the cerebrospinal fluid pressure are increased. For a brief period after discontinuing the maneuver, the following effects have been fairly consistent: heart size, stroke volume, cardiac output, and capillary flow all were greater than normal as the distended veins became rapidly cleared of the accumulated blood. Associated with the increased stroke volume, bradycardia was usually observed. Although the direction of changes of the different variables has become fairly clear, the amount of change in each remains extremely controversial.

The systolic blood pressure during the Valsalva experiment has been reported to fall below the limits of accurate measurement. Other observations have been made which indicate that the systolic pressure progressively increases throughout the period of increased intrathoracic pressure.¹ Dawson² reported an increase to levels of 180 to 200 mm. Hg for a few seconds and then a precipitous fall to

Conducted at the A. A. F. School of Aviation Medicine, Randolph Field, Texas.
Received for publication Dec. 9, 1946.

60 mm. Hg or below, followed by a gradual rise "apparently dependent upon the degree of effort." These findings have been obtained by indirect measurement of the arterial blood pressure and are thus subject to all the variability and errors associated with that method. Direct recording of arterial blood pressure during the Valsalva maneuver by means of the Hamilton optical manometer has been reported by Hamilton, Woodbury, and Harper.³ They described four phases as follows: (a) The blood pressure rose and the pulse became slightly fuller, but the heart rate was unchanged for a few seconds after beginning the maneuver. (b) The pulmonary reservoir became depleted; cardiac filling then became inadequate and the blood pressure fell. As this phase continued, some other factor (vasoconstriction, perhaps) entered into the picture and the blood pressure began to rise gradually. (c) As the strain was discontinued the general blood pressure precipitously fell for 2 to 4 seconds. (d) Very quickly the heart filled more adequately, the pulse pressure increased, systolic and diastolic pressures increased, and the dicrotic notch mounted higher on the descending limb of the pulse curve.

It seems evident that the cardiovascular system was being subjected to a strain during the Valsalva maneuver which should aid in distinguishing individuals with inefficient cardiovascular response to the effects of gravitational forces from those with adequate adaptation. The Flack test (a modified Valsalva maneuver) has been successfully used by MacLean and his associates⁴ in the demonstration of manifestations of orthostatic hypotension. The greatest difficulty in the practical application of a straining maneuver as a circulatory test has been the lack of any function which can be readily and accurately measured as a criterion of the effectiveness of the vasomotor response.

The present study was designed to explore several effects of straining procedures by means of available methods of measurement for the following reasons: (1) to attempt to establish some testing procedure which might facilitate prediction of tolerance to radial acceleration in applicants for pilot training, and (2) to gain information which might aid in understanding the mechanisms by which the cardiovascular system responds to stress.

STUDIES AND RESULTS

The Three Modifications of the Valsalva Experiment Studied.—Descriptions of the three maneuvers and symbols by which they will be identified in the remainder of the report are as follows: (a) The first maneuver consisted of increasing the intrapulmonic pressure 40 mm. Hg after a deep inspiration so that the lungs were well inflated during the strain. The symbol *Vi* is used to represent this procedure. To facilitate observation and recording of intrapulmonic pressure, the subjects were instructed to blow into a tube connected to a water manometer and to sustain a column of water 54 cm. high. This is equivalent to producing an intrapulmonic pressure of 40 mm. of mercury. (b) The second maneuver, designated *Ve*, was similar except that most of the supplemental air was exhaled prior to beginning the strain. (c) The *MI* maneuver, originally described by Wood and Hallenbeck⁵ as a means of increasing tolerance to positive radial accel-

eration, involved exhaling most of the supplemental air and then forcing air through the partially closed glottis, accompanied by vigorous tensing of the voluntary musculature. This maneuver was tested both as a single prolonged effort and also when repeated three times in rapid succession. Measurement of the increase in intrapulmonic pressure during the *MI* procedures required that the subjects be instructed to force air through a fixed leak in the manometer system in lieu of the constricted glottis. In this maneuver the intrapulmonic pressure could be increased to 40 mm. Hg at the onset, but despite every effort the intrapulmonic pressure fell to levels of 20 mm. Hg or below as the lungs became progressively emptied.

The Effect of the Straining Maneuvers on the Position of the Diaphragm and the Size of the Cardiac Silhouette.—To observe the changes in heart size and in the position of the diaphragm, teleroentgenograms were taken on a series of subjects immediately before and during the *Vi* and *Ve* maneuvers. An automatic cassette changer ordinarily used in exposing stereoscopic chest plates was used to allow exposure of the two roentgenograms in rapid succession without changing the position of the subject.

Each subject stood facing the automatic cassette changer. The water manometer was placed in his line of vision and the metal mouthpiece on the tube leading to the manometer was held between his teeth. He took a deep breath and held it while a roentgenogram was exposed. Without inhaling or exhaling he blew into the tube, elevating the water in the manometer 54 cm. and retaining it at this level. The cassette changer was operated and after twenty seconds another roentgenogram was exposed. In this way the quantity of air within the lungs was the same during the exposure of the two x-ray films except for the gaseous interchange with the blood during the twenty-second strain. It required only 13 cm. of air to displace the fluid in the manometer which would not appreciably affect the height of the diaphragm. A similar technique was used in the study of the *Ve* maneuver except that air hunger prevented prolonged straining and the second roentgenogram was taken seven seconds after the intrapulmonic pressure was increased. In the case of the *MI* maneuver, the escape of air from the lungs produced a progressive movement of the heart and diaphragm. The effects of this maneuver were observed by means of the fluoroscope.

To facilitate comparison of the roentgenograms taken before and during the maneuvers, tracings were made from both x-ray plates on the same sheet of paper. Landmarks such as the upper thoracic vertebral spines and the costo-vertebral articulations were superimposed, since these structures apparently moved very little during the respiratory movements. The areas of the two cardiac silhouettes were measured by means of a planimeter. Visualization of the cardiac border in the region of the apex of the heart was improved in several experiments by inflating the cardia of the stomach with gas in one of three ways: (a) by having certain subjects voluntarily swallow air, (b) by drinking a carbonated beverage and avoiding eructation, or (c) by injecting air through a Miller-Abbott tube when intragastric pressures were being recorded.

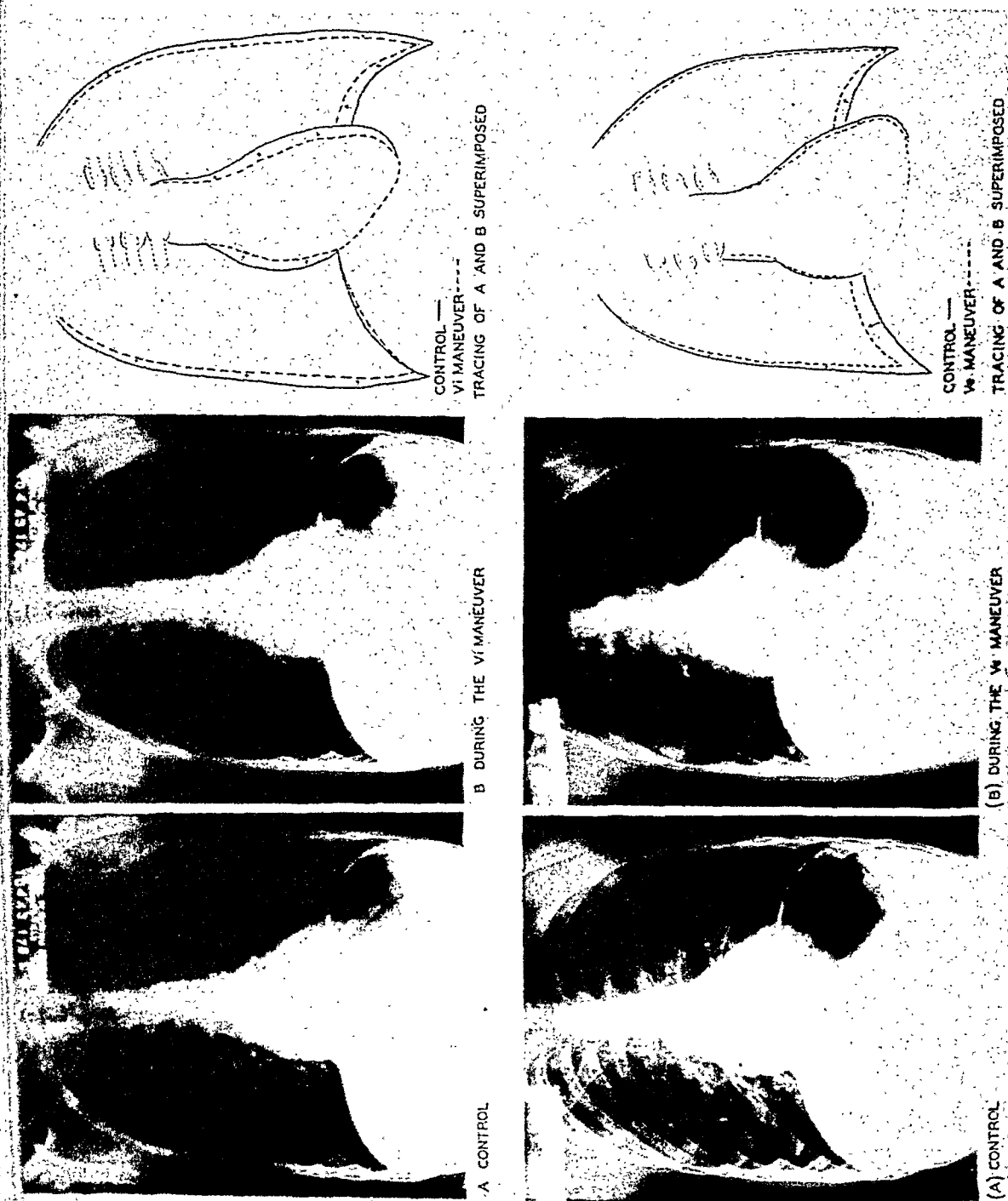


Fig. 1.—Tracings were made of the cardiac silhouette on roentgenograms taken immediately before performing the V_i and V_e maneuvers (solid line). On the same piece of paper, the cardiac silhouette was superimposed from the roentgenogram taken during the corresponding maneuver (broken line). Inflation of the cardia of the stomach with gas in several subjects facilitated observation of the cardiac border in the region of the apex.

Results: Forty-two pairs of roentgenograms were made on thirteen healthy young male subjects. During the *Vi* maneuver, the diaphragm was elevated during the strain in about half of the cases (Fig. 1) and the area of the cardiac silhouette was decreased on the average by 20 sq. cm. (17.1 per cent). The diaphragm was invariably displaced cephalad during the *Ve* maneuver and reduction in the area of the cardiac silhouette was less marked, averaging 14.7 sq. cm. (10.4 per cent). Fluoroscopic examination during the *MI* maneuver revealed that the diaphragm continued to move upward so long as air was expelled from the lungs. The dome of the diaphragm rose behind the heart obscuring more and more of the heart shadow. No measurements of cardiac area were attempted during this maneuver.

The Relation of Intrapulmonic Pressures to Intragastric Pressures During the Three Maneuvers.—The intrapulmonic pressure was measured by recording the pressure maintained by the subject in the manometer system by means of a Hamilton optical manometer. The various types of recording apparatus used in the present series of experiments have been described elsewhere.^{6,7} Intragastric pressures were recorded by a second Hamilton manometer connected to a Miller-Abbott tube, the balloon of which was in the cardia of the stomach. The location of the tip of the tube was checked in each case by means of a flat plate of the abdomen. The intragastric pressure was always 4 to 7 mm. Hg. above atmospheric pressure and was directly affected by respiratory activity (Fig. 2). The increases in intragastric pressure during the Valsalva maneuvers were measured from the basal level which appeared during the relaxation associated with expiration. There was no evidence of interference with the accuracy of the recordings by gastric peristalsis.

Results: Simultaneous recordings of the intrapulmonic and intragastric pressures were obtained during the performance of the three maneuvers by seven subjects (Fig. 2). During the *Vi* maneuver, the average increase in intragastric pressure was between 29 and 32 mm. Hg while the intrapulmonic pressure was held at 40 mm. of mercury. Since the diaphragm cannot exert force in the upward direction, it was not considered likely that the pressure in the chest could be higher than in the abdomen. The discrepancy could be explained if the intrathoracic pressure were 8 to 11 mm. Hg less than the intrapulmonic pressure because of the elastic tension being exerted by the lungs. After deep inspiration the intrathoracic (intrapleural) pressure has been reported to be as much as -30 mm. of mercury.⁸ During the *Ve* maneuver, the average intragastric pressure in these same subjects ranged between 45 and 60 mm. Hg (average 55 mm. Hg) when the intrapulmonic pressure was maintained at 40 mm. of mercury. Satisfactory performance of the *MI* maneuver produced intragastric pressures of 55 to 74 mm. Hg, while the intrapulmonic pressure was gradually falling off from 40 to 20 mm. Hg, or below. The intrathoracic pressure was probably only about 2 to 3 mm. Hg less than intrapulmonic pressure due to the degree of deflation of the lungs during the *Ve* and *MI* maneuvers.⁸ The high intragastric pressures in these two maneuvers was attributed to the fact that at the beginning of the maneuver, the diaphragm was high and compression of the air within

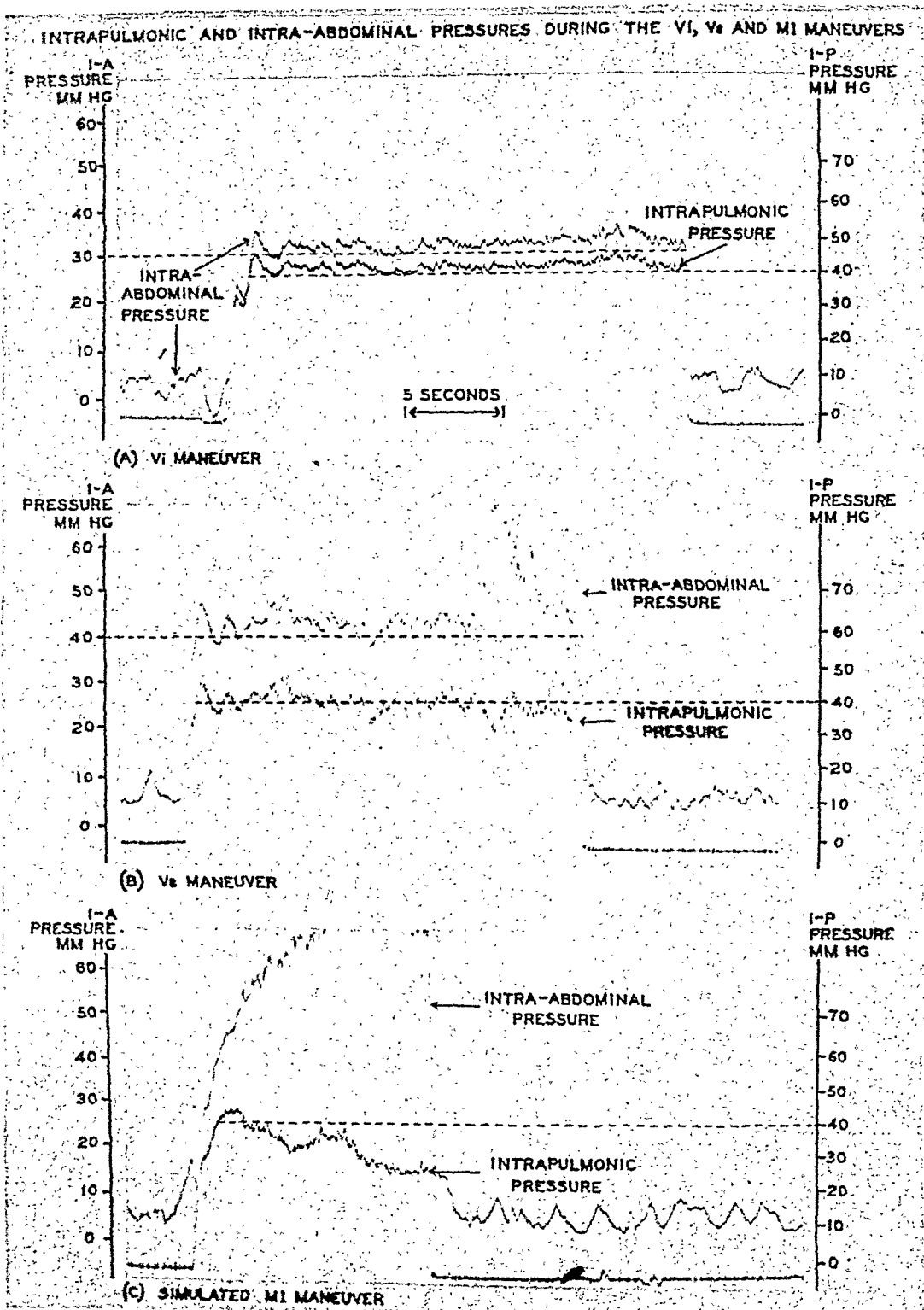


Fig. 2.—Simultaneous recordings of the intrapulmonic and intragastric pressures revealed that increasing the intrapulmonic pressure 40 mm. Hg with the lungs inflated (Vi maneuver) produced an increase in intragastric pressure of about 30 mm. of mercury. During the V_e and M_I maneuvers, performed after forced exhalation, the intragastric pressure equaled or exceeded the intrapulmonic pressure.

the chest was accomplished by increasing intra-abdominal pressure by an amount sufficient to produce further elevation and stretching of the diaphragm. This differential in pressure between the abdomen and thorax should facilitate the flow of blood from the splanchnic venous reservoirs to the right side of the heart.

The Response of Arterial Blood Pressure, Venous Pressure, and Finger Volume During the Maneuvers.—Arterial and venous pressures were recorded on subjects in the seated position by means of a bank of Hamilton optical manometers. The intra-arterial pressure was recorded directly from within the brachial artery and the venous pressure in the arm was measured from an antecubital vein. The level at which the arm rested was adjusted in each case until the points of the intravascular needles were approximately 5 cm. below the sternal notch. Venous pressure from the dependent lower extremities was recorded from a dorsal vein of the foot or from a superficial vein in the lower part of the leg. Records were obtained of the changes in the volume of the index finger by means of simple, pneumatic, finger plethysmographs carefully fitted to the index finger. The plethysmograph was connected by small-bore rubber tubing to a rubber tambour on which a mirror was eccentrically mounted.

The arterial, venous, and plethysmographic records were obtained by photographing the deflections of the mirrors on the Hamilton manometers and finger plethysmograph tambour by means of a 12 cm. camera.⁷

Arterial pressures were recorded on sixteen subjects during one or more of the maneuvers, and in six of these venous pressures from the upper extremity were also obtained. Simultaneous records of intrapulmonic pressure, intragastric pressure, and venous pressures in the arm and leg were recorded in seven subjects. A total of seventy-three determinations of the changes in the venous pressure in the arm were made during the various maneuvers. The rate of increase in venous pressure in mm. Hg per second was calculated by dividing the amount of increase in the venous pressure by the duration of the progressive increase.

Results: Direct recording of arterial pressure during *Vi* maneuvers revealed changes similar to those described by Hamilton and co-workers.³ An example of a typical response is presented (Fig. 3). Immediately after the maneuver was begun, the systolic and diastolic pressures increased for three or four beats. This has been attributed to the direct effect of the increased pressure within the chest on the heart and lungs. The systolic, diastolic, and pulse pressures were then reduced, presumably as a result of depletion of the blood within the pulmonary circulation and during this period the pulse rate usually increased. The gradual increase in arterial pressure during the remainder of the maneuver has been attributed to compensation on the part of the peripheral vascular system in the form of vasoconstriction. Sudden release of the intrapulmonic pressure was immediately followed by a brief but precipitous fall in blood pressure and then a very high systolic and pulse pressure associated with bradycardia. An increase in finger volume occurred during the maneuver (Fig. 3) and when the maneuver had been completed, for a period of about fifteen seconds, the volume in the finger was often less than it had been preceding the strain. This may be an indication that peripheral vasoconstriction occurred during the strain. Dur-

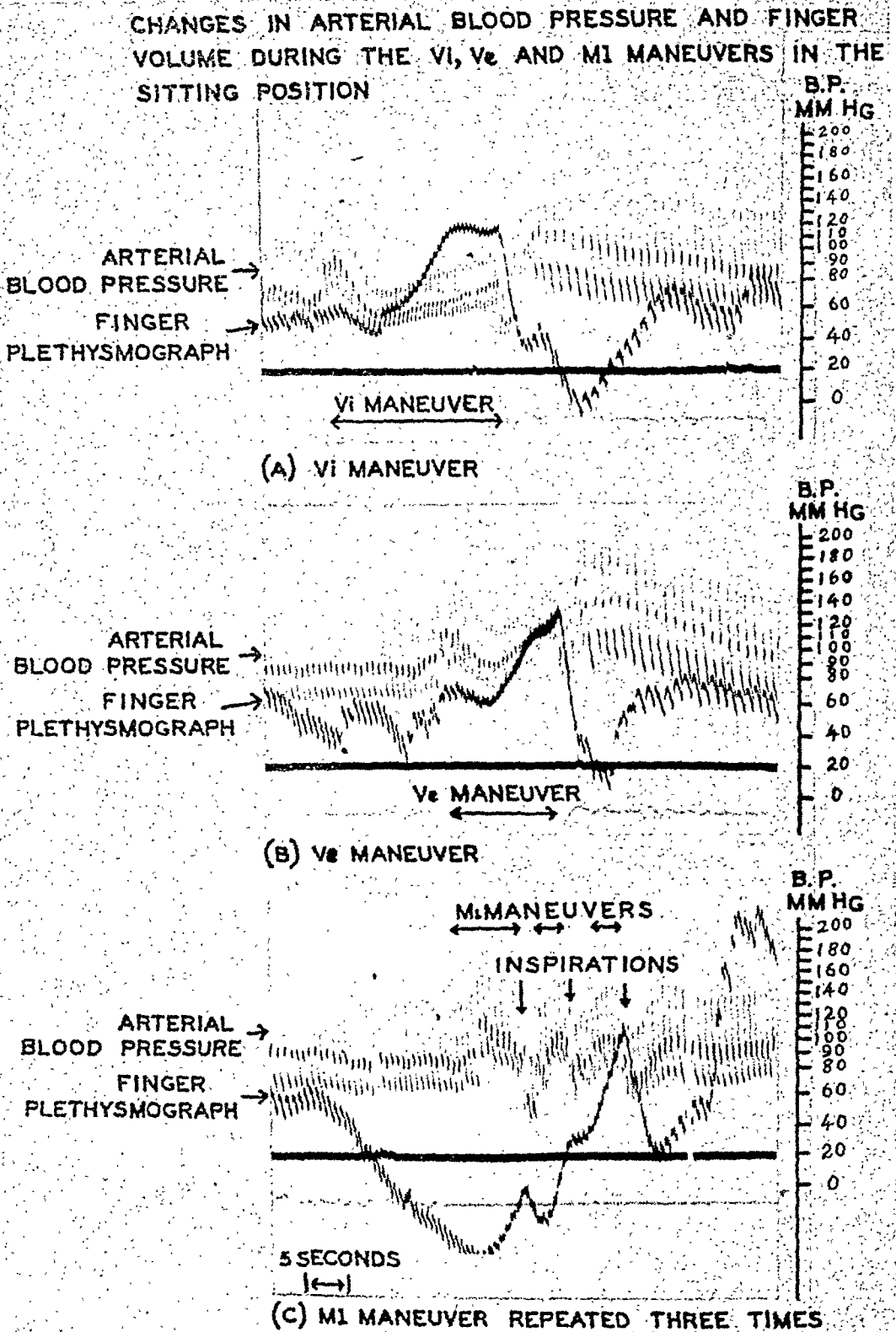


FIG. 3.—Direct arterial blood pressure, recorded by means of a Hamilton optical manometer, and changes in finger volume, recorded by means of a pneumatic plethysmograph on the right index finger, were obtained during three modifications of the Valsalva experiment.

CHANGES IN INTRAPULMONIC, INTRA-ABDOMINAL AND VENOUS PRESSURE IN THE ARM WITH THE V_i , V_e AND M_I MANEUVERS.

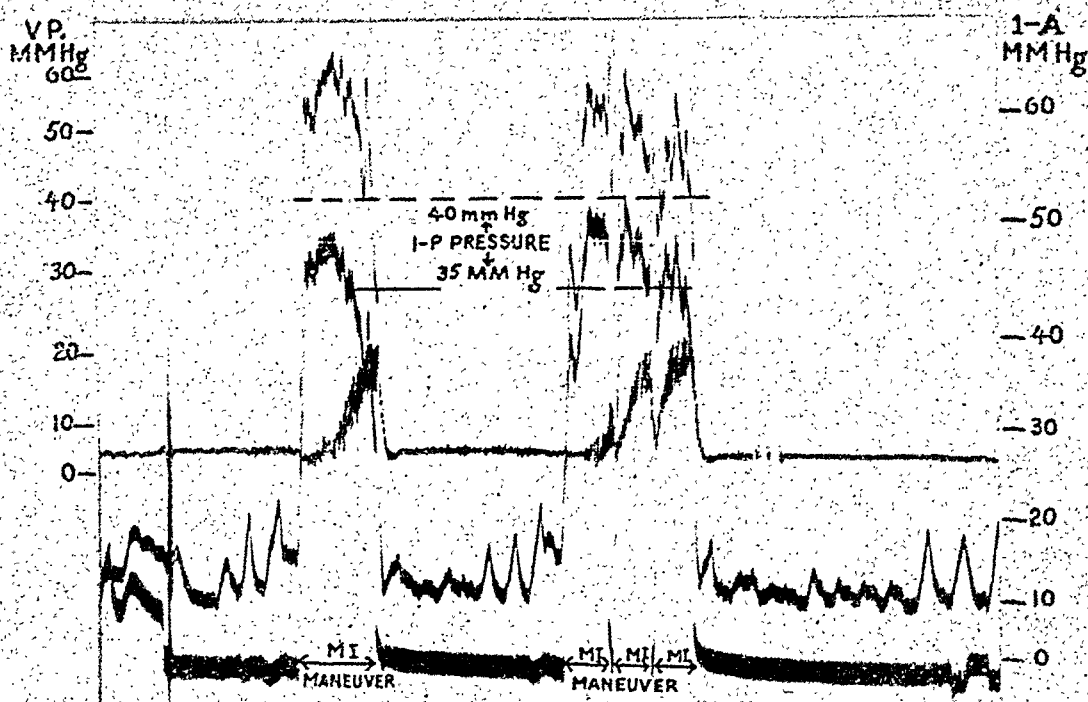
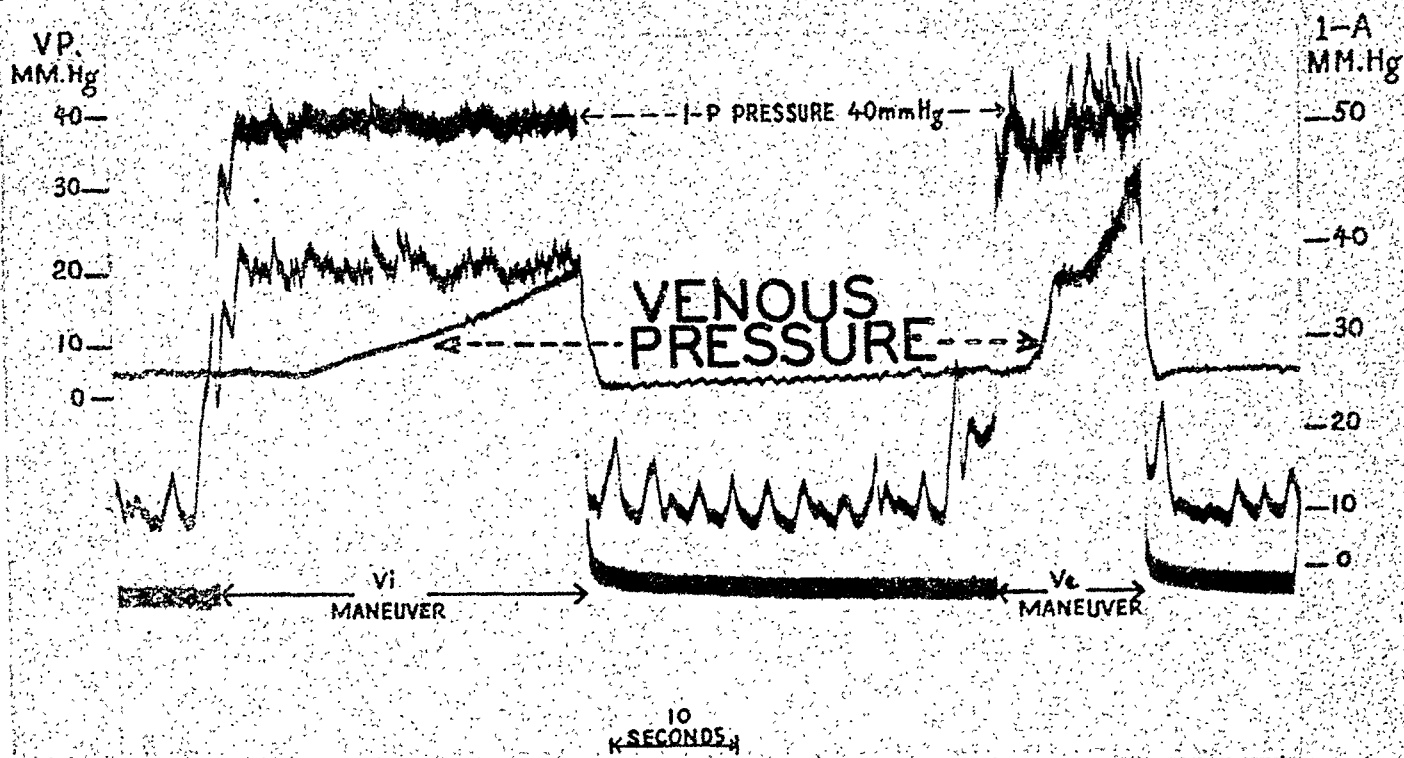


Fig. 4.—Venous pressure recordings from an antecubital vein in a seated subject during the three types of straining maneuvers in this case reveals the lag in the onset of the rise of venous pressure after the intrapulmonic and intragastric pressures were suddenly increased. The difference in the slope of the progressive increase in venous pressure during the three maneuvers is apparent.

ing the V_e maneuver these same changes may be identified, but the arterial blood pressure was maintained at a higher level during the strain. This may have been due to the fact that there was a gradient in pressure from the abdomen toward the thorax which provided more adequate venous return during this maneuver than during the V_i maneuver. MI maneuvers, either single prolonged efforts or repeated efforts in rapid succession, increased the arterial blood pressure levels during the straining effort, but during the inspiratory gasps between efforts the arterial pressure fell precipitously. During these maneuvers, the finger volume increased progressively with each effort (Fig. 3).

The records of changes in venous pressure during the performance of the modifications of the Valsalva maneuver revealed a gradual increase in venous pressure when the pressure within the body cavities was suddenly increased. In the upper extremities, there was frequently a lag before the onset of the rise in pressure (Fig. 4), while in the lower extremities the onset of the increase in venous pressure often occurred as a result of the forced inspiration or expiration preceding the actual maneuvers. This was attributed to the fact that ante-cubital veins at heart level were not distended with blood and required additional filling before a measurable increase in venous pressure occurred. Since the subjects were in the sitting position, the veins in the legs were probably fairly well distended with blood during the entire experimental period. Evidence in favor of this concept was found in the fact that the venous pressure in the legs varied with the changes in intra-abdominal pressure associated with respiratory activity. This was not observed in venous pressure recordings from the upper extremity.

The slope of the increase in venous pressure was usually more regular and linear during the V_i maneuver than during the V_e and MI modifications (Fig. 4). The rapid oscillations occurring during the latter portion of the V_e and MI maneuvers were due to muscular tremors associated with intensive straining. Due to the confusion resulting from having two or more records with different calibration scales appearing in a single illustration, the relation of the changes in venous pressure of the arm and leg to the increase in intrapulmonic and intra-abdominal pressure in a typical subject was illustrated by plotting these functions at two second intervals according to a single calibration scale (Fig. 5). The relation of changes in venous pressure to the pressures within the trunk are fairly typical except that venous return from the arm was probably re-established during the last portion of the MI maneuver in this case. In no other experiment did the venous pressure increase exceed the pressure within the corresponding body cavity by more than 2 or 3 mm. of mercury.

The rate of increase in venous pressure during the maneuvers computed in mm. Hg per second seemed to be the most promising test used in this series. The results of this measurement can be expressed as a numerical score having some theoretical relation to the vasomotor function of the individual. Among the group of subjects studied, there seemed to be some tendency for similar results to be obtained in the same subject on repeated determinations (Table I). The possibility of standardizing the procedure seemed good and the intricacy of the apparatus does not seem prohibitive. It is important to emphasize that

RELATION OF CHANGES IN VENOUS PRESSURE OF THE ARM AND LEG TO THE INCREASE IN INTRAPULMONIC AND INTRA-ABDOMINAL PRESSURE DURING THE V_i , V_e AND M_i MANEUVERS IN THE SITTING POSITION.

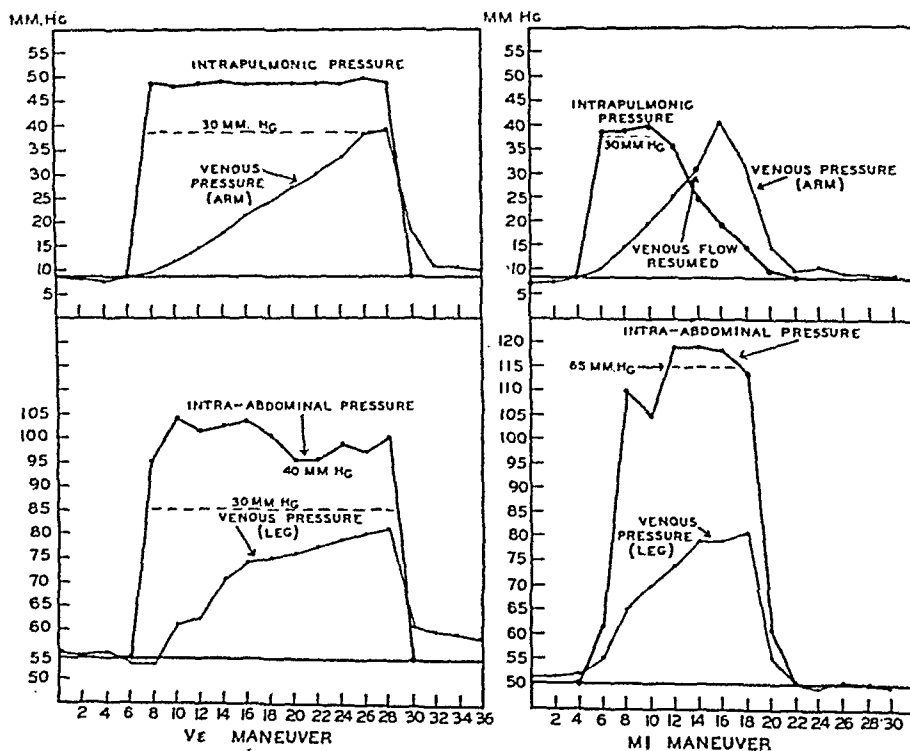
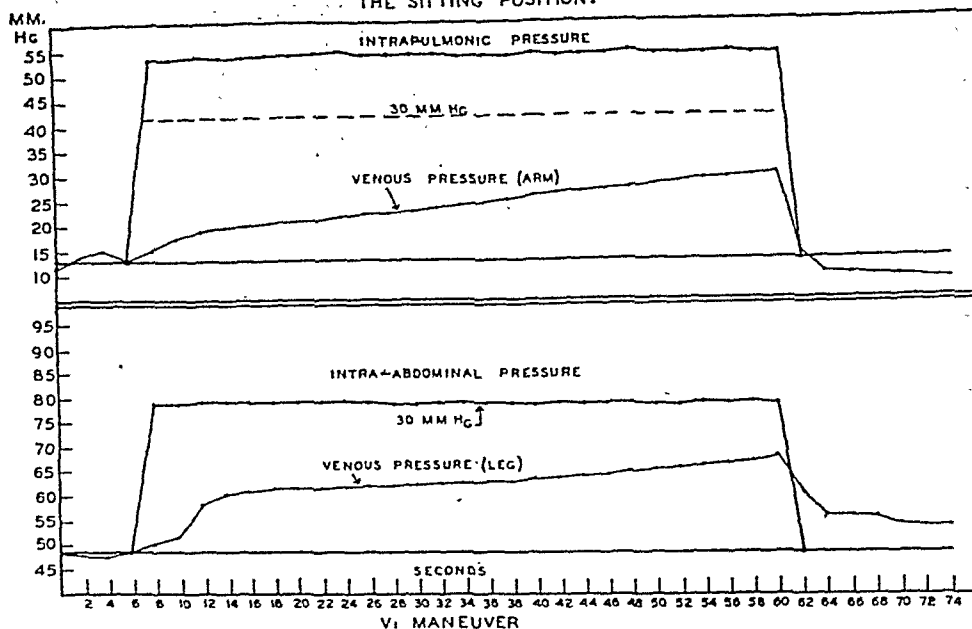


Fig. 5.—By plotting the intrapulmonic and antecubital venous pressure and intragastric and venous pressure in the lower leg at 2-second intervals according to a single calibration scale, the relation of the venous pressure increase to the pressure within the corresponding body cavity is more clearly illustrated.

in the absence of carefully conducted experiments designed to establish the reliability and validity of such a test, no reliable statement can be made concerning its usefulness.

The theoretical relation of the rate of rise of venous pressure to the vasoconstrictor function of the subject is based on the following assumptions: (1)

TABLE I. RATE OF VENOUS PRESSURE INCREASE DURING THE VI MANEUVER (ANTECUBITAL VEIN)

SUBJECT	DURATION OF MANEUVER IN SECONDS	DURATION OF VENOUS PRESSURE INCREASE IN SECONDS	VENOUS PRESSURE INCREASE IN MM. HG	RATE OF VENOUS PRESSURE INCREASE IN MM. HG PER SECOND
1	32	32	26	0.81
	32	18	27	1.50
	32	24	24	1.00
	22	22	28	1.27
2	34	34	17	0.50
	40	40	23	0.57
	36	36	25	0.70
	28	28	15	0.53
	28	28	16	0.57
3	30	30	14	0.47
	32	32	12	0.38
	36	36	10	0.28
	32	32	7	0.22
	30	30	8	0.27
4	28	28	17	0.61
	30	30	14	0.46
	32	30	13	0.43
	33	33	16	0.49
5	20	20	32	1.60
	22	22	34	1.54
	22	22	30	1.36
6	34	34	4	0.12
	30	30	5	0.17
	30	30	5	0.17
7	28	28	20	0.71
	28	28	26	0.90
8	20	16	38	2.38
	22	22	29	1.32
	22	22	25	1.14
9	26	26	7	0.27
10	26	26	23	0.89
11	56	56	17	0.30
	52	52	20	0.39
12	36	36	24	0.66
Range	20-56	16-56	4-38	0.12-2.38
Average	30.6	29.8	19.1	0.74

The presence of functional valves in normal veins prevents retrograde flow of venous blood into the extremities. This concept is substantiated by the observation that the venous pressure increased slowly when the intrathoracic and intra-abdominal pressures were suddenly elevated. (2) Under these conditions all

the blood that enters the veins has passed through the small vessels from the arterial side. (3) If venoconstriction does not occur, the rate of rise of venous pressure should depend primarily upon the rate at which blood passes through the capillaries and arteriovenous shunts. If venoconstriction occurs, this might accelerate the increase in venous pressure but may be considered a part of the vasomotor response.

CHANGES IN ARTERIAL BLOOD PRESSURE AND FINGER VOLUME RESULTING FROM THE V_i AND V_e MANEUVERS PERFORMED DURING THE ONSET OF CIRCULATORY COLLAPSE.

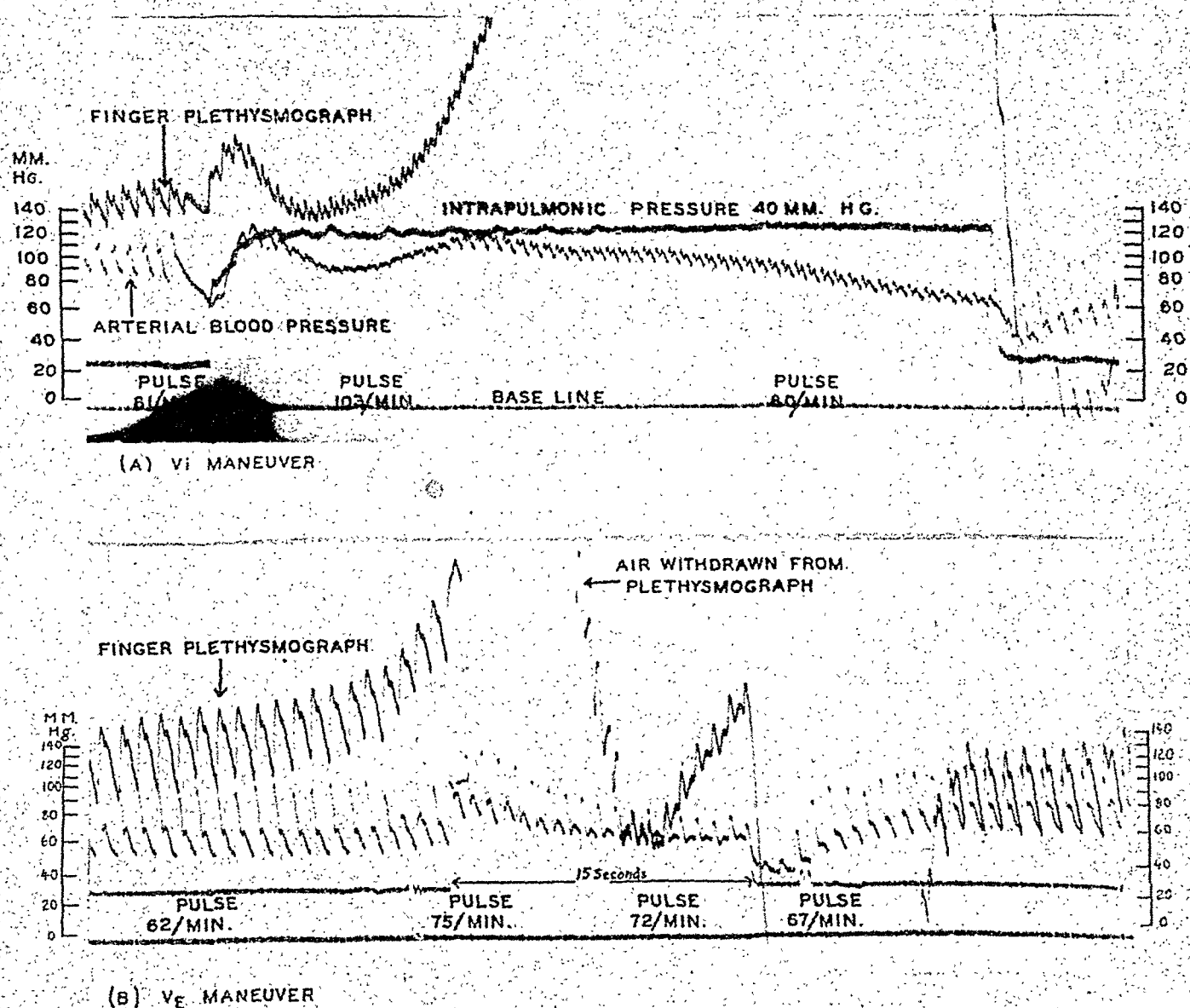
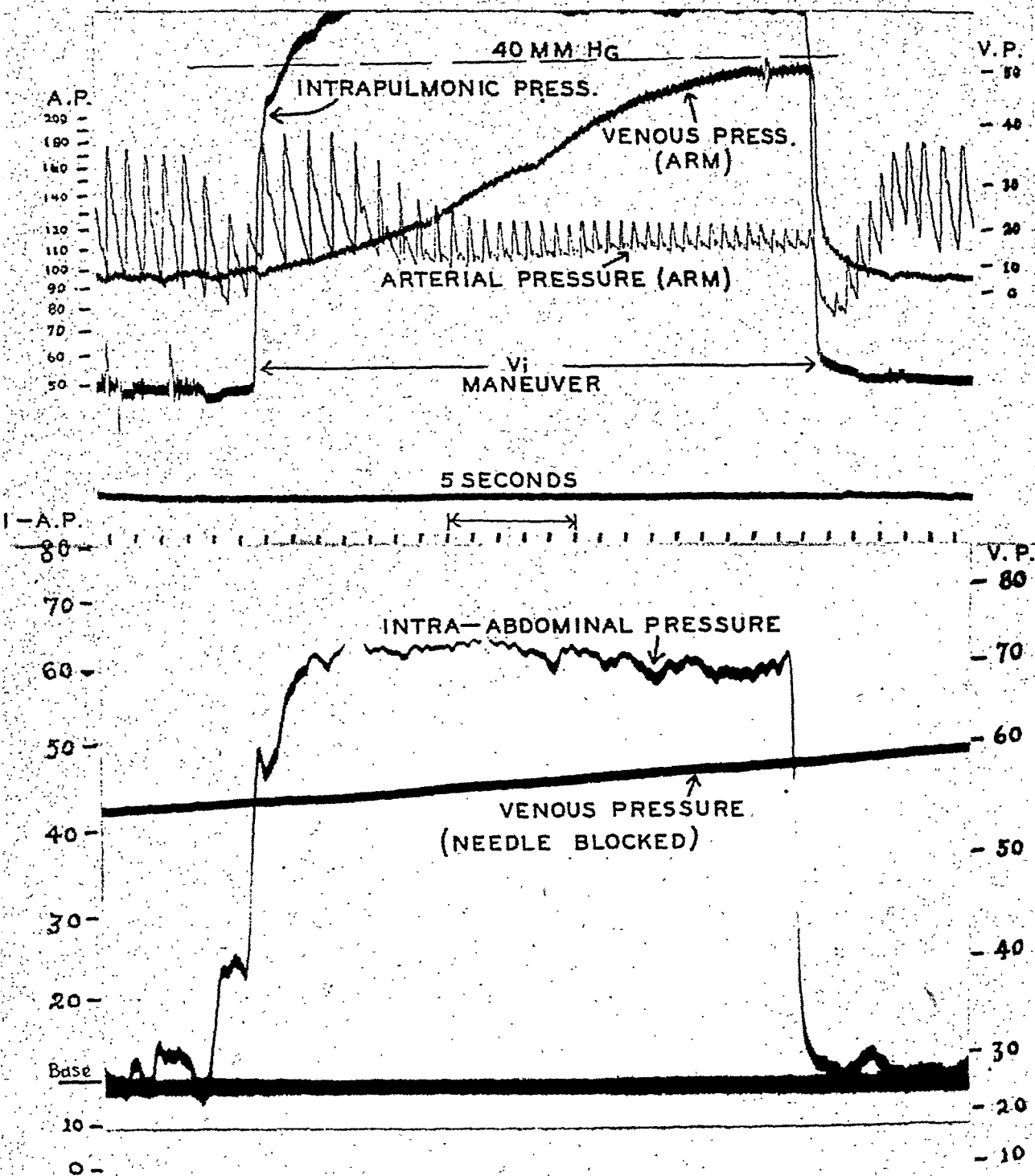


Fig. 6.—Recordings of direct brachial arterial blood pressure and changes in the volume of the index finger in a seated subject during the onset of circulatory collapse indicate the type of response seen when the circulatory adjustment during the straining maneuvers is inadequate.

Arterial and Venous Pressure Recordings in Subjects Having Poor Circulatory Compensation to Increased Intrathoracic Pressure.—In the course of this study it was possible to observe the response of fifteen subjects during circulatory

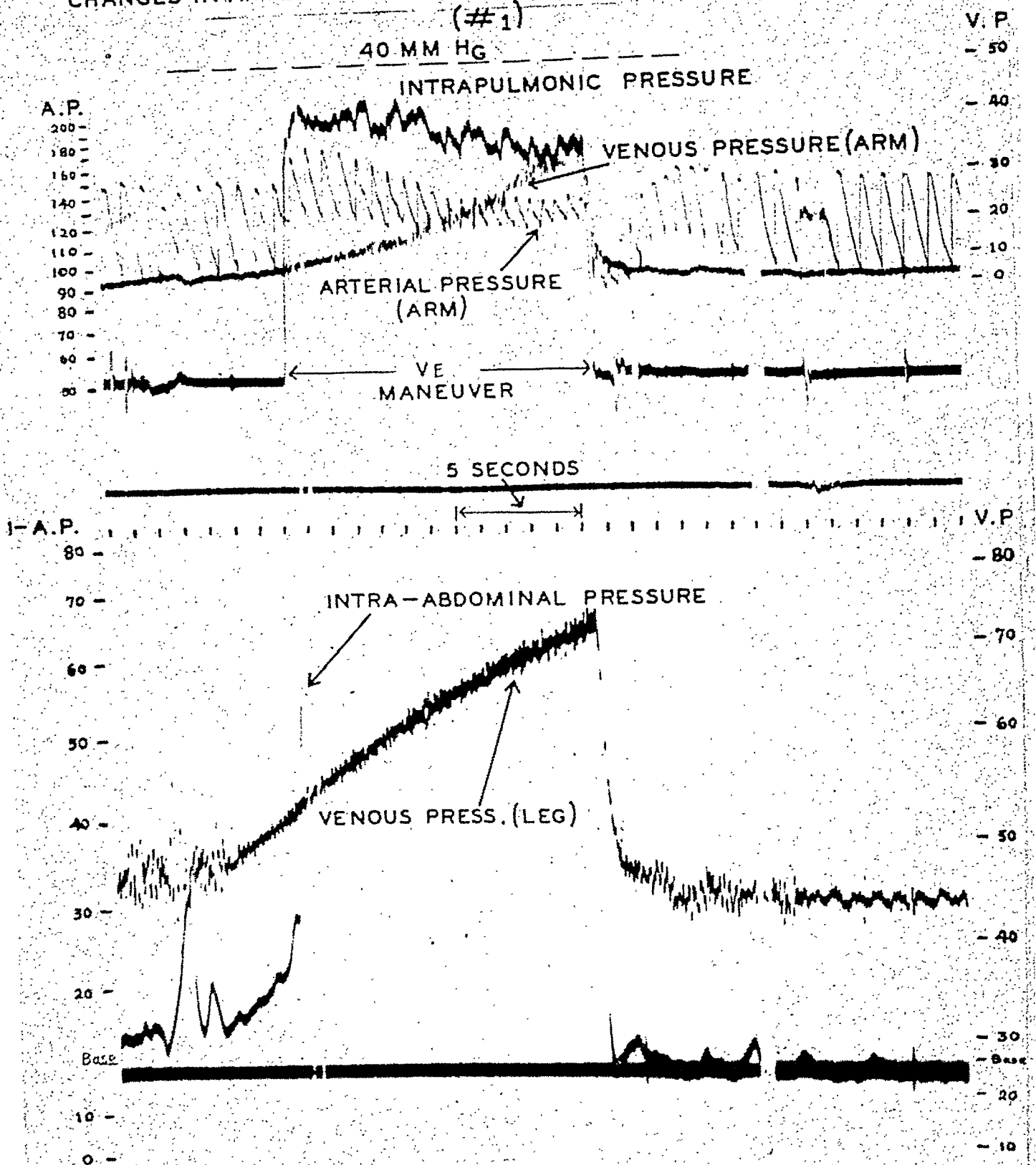
CHANGES IN ARTERIAL AND VENOUS PRESSURE DURING THE V_i MANEUVER # 1



A.

Fig. 7.—Simultaneous recordings of direct arterial blood pressure, intrapulmonic and intragastric pressures, and venous pressure from the arm and leg in a subject with a history of mild orthostatic hypotension. The initial response A and B) bears marked resemblance to that revealed in Fig. 6. After three straining maneuvers had been accomplished, the response to the V_i and V_e maneuvers resembled more closely the response seen in the normal subjects (C and D).

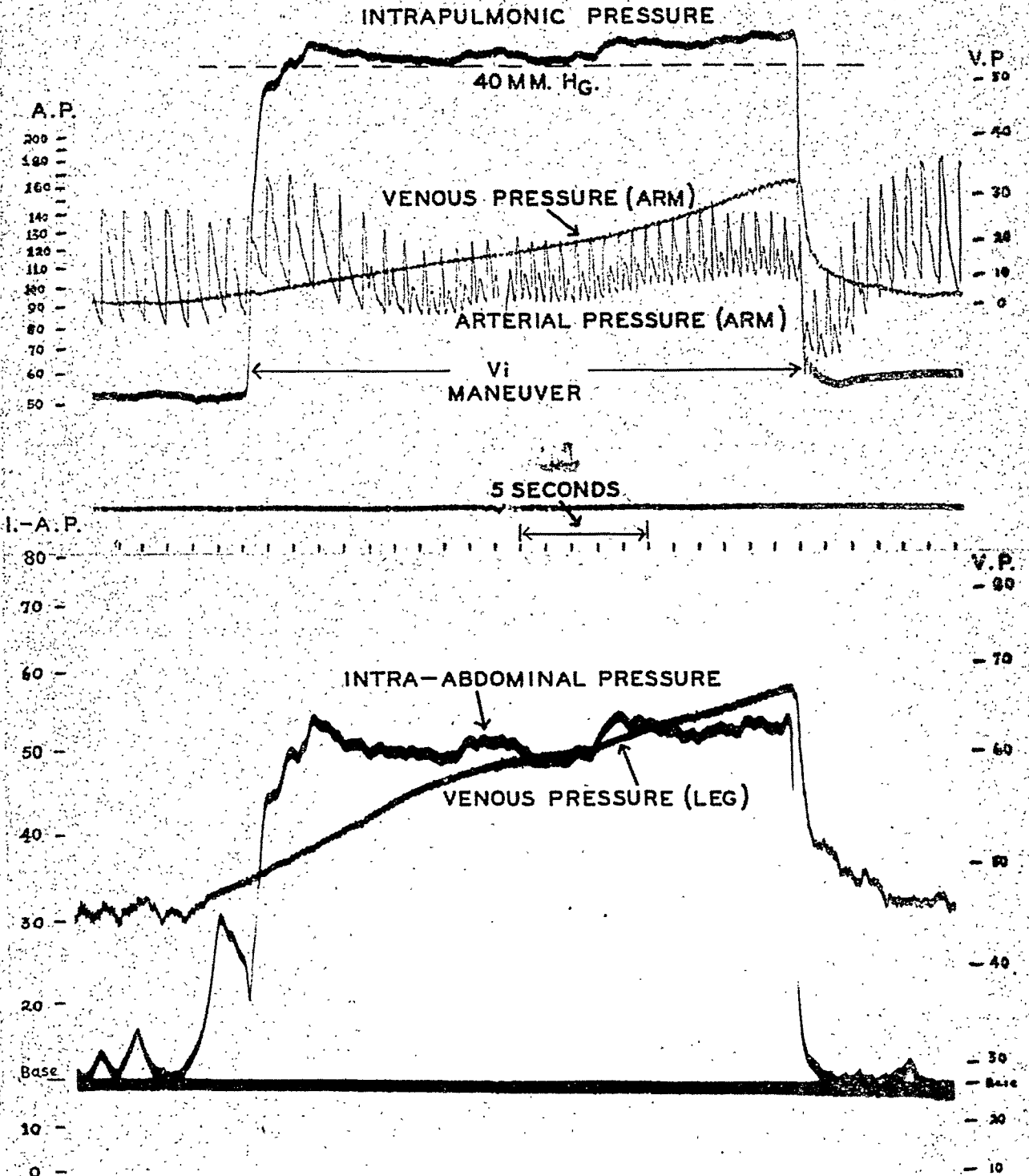
CHANGES IN ARTERIAL AND VENOUS PRESSURE DURING THE V_E MANEUVER (#1)



B.

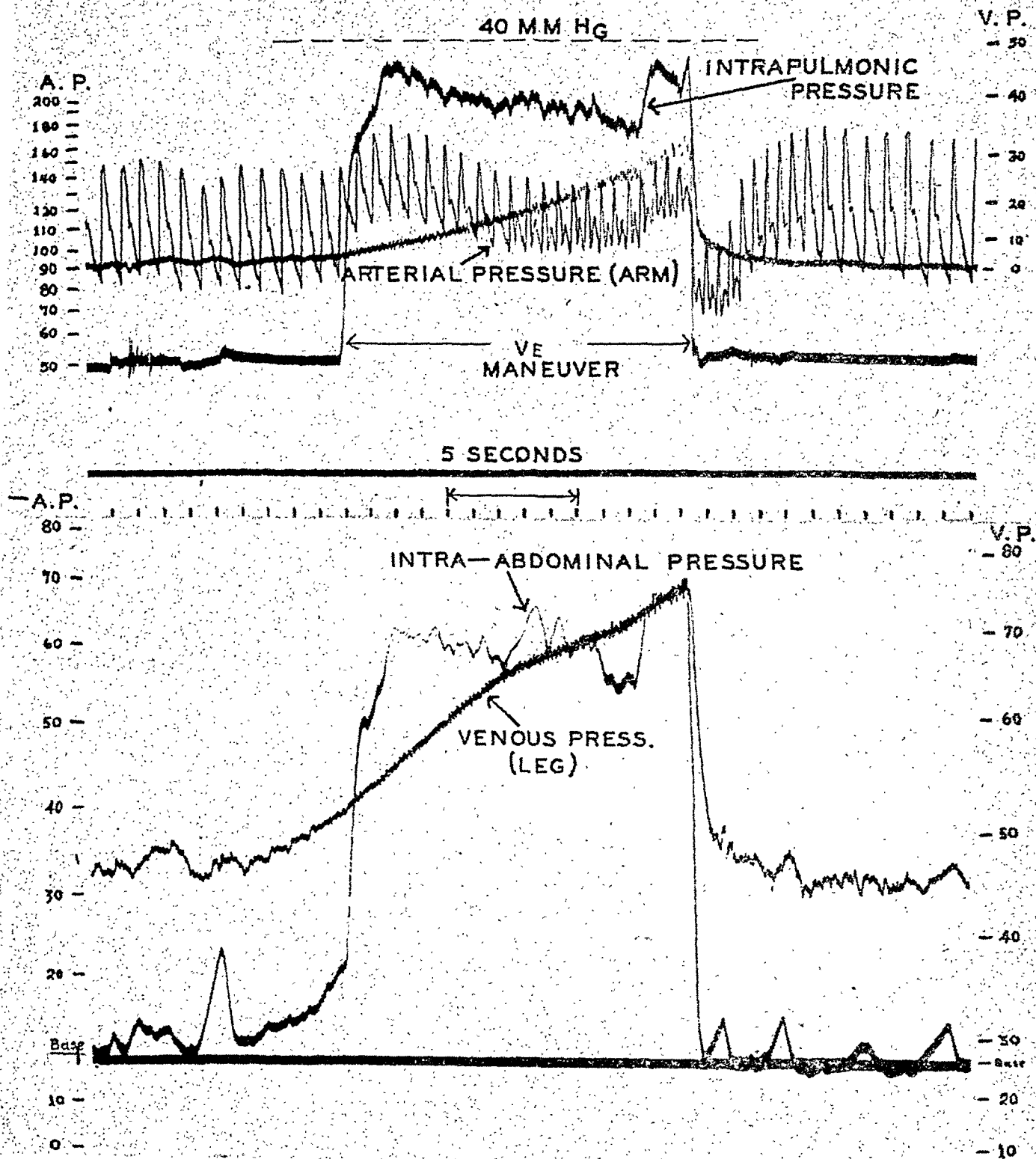
Fig. 7.—For legend, see opposite page.

CHANGES IN ARTERIAL AND VENOUS PRESSURE DURING THE Vi MANEUVER (#2)



C.

Fig. 7.—For legend, see page 412.

CHANGES IN ARTERIAL AND VENOUS PRESSURE DURING THE V_E MANEUVER
2.

D.

Fig. 7.—For legend, see page 412.

collapse apparently resulting from mechanical stimulation of the brachial arterial wall.⁹ In one of these cases blood pressure recordings were obtained while the subject was performing a V_i and a V_e maneuver during the onset of the circulatory collapse (Fig. 6). In both of these maneuvers, the blood pressure response was obviously different from that previously observed in the normal subjects. The blood pressure and pulse pressure were significantly reduced and compensation during the maneuvers failed to occur. The heart rate did not increase significantly and the final systolic blood pressure was but slightly over 60 mm. of mercury. The recovery periods following the maneuvers were not accompanied by an overcompensation during which the systolic blood pressure was greater than preceding the strain. Since this subject was unable to remain erect without severe dizziness and sensation of impending loss of consciousness, it seems reasonable to classify the observed response as the result of inadequate peripheral vascular adjustment to the strain of the V_i and V_e maneuvers.

A series of interesting records was obtained on a subject having a history of occasional bouts of dizziness and loss of vision on suddenly standing erect after having been relaxed in the sitting or reclining position. On this subject, simultaneous recordings were obtained of arterial blood pressure, venous pressure from the upper and lower extremities, and intrapulmonic and intragastric pressures. A series of twelve straining maneuvers were performed during this experiment. The first two records consisted of V_i and V_e maneuvers (Fig. 7, *A* and *B*) during which the arterial blood pressure response was similar to that observed in the subject developing circulatory collapse (Fig. 6). The rate of the venous pressure increase during the V_i maneuver was more rapid than was encountered among the remainder of the subjects (2.38 mm. Hg per second, Subject 8, Table I). In the series of twelve maneuvers the fourth and fifth maneuvers were also V_i and V_e maneuvers (Fig. 7, *C* and *D*). The arterial response was by this time comparable to that observed in the average subject, since the pulse pressure was fairly well maintained and compensation in blood pressure occurred during the maneuvers. The rate of rise in venous pressure in the arm was obviously less than that observed during the first V_i maneuver.

DISCUSSION

The principal objective of the present series of studies was an attempt to devise some test of the efficiency of the cardiovascular system in compensating for the stress applied by means of modifications of the Valsalva experiment. It was assumed that individuals exhibiting poor response to such stress would also display other symptoms of inefficient cardiovascular adjustments. If it were possible to produce a satisfactory measurement of cardiovascular response to the Valsalva maneuver, this test might be useful not only in predicting tolerance to positive radial acceleration, but in general clinical practice and research. With this in mind, certain criteria were established to aid in deciding whether the methods tested might be suitable for further study or should be discarded. These criteria, which, in fact, describe an "ideal" test were as follows: (1) the measurement should be objective, preferably in terms of a numerical scale;

(2) the apparatus required to perform the test should be simple and readily available; (3) the test should be easy to perform and should not produce pain or discomfort; (4) changes in the measured function should be the direct result of the stress applied, with as few complicating factors as possible; (5) the response of various subjects should be reproducible on repeated testing of the same subjects under the same conditions; and (6) there must be a close relation between the response of the individual to the test and the state of his vasomotor system. The favorable and unfavorable aspects of the various measurements are summarized in terms of these criteria.

The Valsalva experiment is a convenient type of test because it requires only a simple manometer. The results of the experiments described previously indicated that increased intrapulmonic pressure when the lungs are well inflated (V_i maneuver) provides a greater stress on the circulation than the other two modifications. This assertion is based on the observed changes in cardiac size and arterial and venous blood pressure. The V_e and M maneuvers apparently provide a favorable gradient in pressure between the abdominal and thoracic cavities, which facilitates venous return from the splanchnic circulation.

Reduction in the size of the cardiac silhouette occurred in all subjects tested while performing the V_i and V_e maneuvers. There were obvious errors in measurement of considerable magnitude which seemed to preclude successful use of this type of measurement. For example, the magnitude of changes in the size of the cardiac silhouette in different subjects might be due to difference in the phase of the cardiac cycle at which the roentgenogram was exposed, differences in the configuration and position of the heart, and the habitus of the individual. Experience indicated that the results on repeated testing were not satisfactorily reproducible.

The records of the arterial blood pressure were probably the best available indicator of the response of the individual. Unfortunately, the changes cannot be accurately measured by means of a sphygmomanometer, the apparatus required to record these changes is bulky, difficult to maintain, and unpleasant for the subject. Further, the fact that the recorded systolic blood pressure during control periods was frequently above 140 mm. Hg after the arterial puncture strongly suggested that there had been changes in the cardiovascular system due to the use of the measuring device.

The changes in finger volume during the maneuver as recorded by means of a finger plethysmograph were expected to be of some value. However, in this series the greatest difficulty was found to lie in standardization and in providing a simple but accurate measure of the volume changes.

The changes in venous pressure associated with the V_i maneuver offered some promise. As previously explained, the rate of increase of venous pressure during the maneuvers should be dependent in large part upon the rate at which blood passed through the small vessels from the arterial to the venous side in the extremity being tested. This measurement provides a numerical and objective result. Venepunctures are not excessively unpleasant but may affect the result through excitement or anticipation. The apparatus required is not simple be-

cause it is deemed necessary to obtain an actual record of the changes rather than depend on observing the meniscus in a venous pressure manometer. The fact that one subject revealed a rapid rise in venous pressure associated with a poor arterial blood pressure response and slow rate of increase when the response was improved is encouraging but far from conclusive.

CONCLUSIONS

1. A study has been made of the effect of three modifications of the Valsalva experiment on the size of the cardiac cycle, the position of the diaphragm, the arterial blood pressure, the venous pressure in the upper and lower extremities, and the volume of the index finger.

2. The measurements were conducted in an attempt to devise a test of the response of the peripheral circulation under stress.

3. The rate of raise of venous pressure in the upper extremity resulting from a sudden increase in intrathoracic pressure after a deep inspiration appears to have some value as a measure of the state of the small blood vessels below the point of measurement. Further study of the reliability and validity of this test is required before arriving at a decision as to its value.

The aid and advice of Lieutenant Colonel C. E. Kossmann, and Captain D. H. Cahoon Medical Corps, United States Army, and Sergeant Walter Wagner, United States Army, are most gratefully acknowledged.

REFERENCES

1. Liedholm, K.: The Venous Pressure in Valsalva's Experiment, *Acta med. Scandinav.* 106:1, 1939.
2. Dawson, P. M.: The Physiology of Physical Education, Baltimore, 1935, Williams & Wilkins Company.
3. Hamilton, W. F., Woodbury, R. A., and Harper, H. T.: Physiological Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, *J. A. M. A.* 107:853, 1936.
4. MacLean, A. R., Allen, E. V., and Magath, T. B.: Orthostatic Tachycardia and Orthostatic Hypotension: Defects in the Return of Venous Blood to the Heart, *AM. HEART J.* 27:145, 1944.
5. Wood, E. H., and Hallenbeck, G. A.: Voluntary (Self-protective) Maneuvers Which Can Be Used to Increase Men's Tolerance to Positive Acceleration, *Federation Proc.* 5:115, 1946.
6. Hamilton, W. F., Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal, *Am. J. Physiol.* 107:427, 1939.
7. Cahoon, D. H., Rushmer, R. F., and Kossmann, C. E.: Modification of Hamilton Optical Manometer, *J. Lab. & Clin. Med.* 30:541, 1945.
8. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, 1939, Williams & Wilkins Company, p. 486.
9. Rushmer, R. F.: Circulatory Collapse Following Mechanical Stimulation of Arteries, *Am. J. Physiol.* 141:722, 1944.

Clinical Reports

SHRAPNEL WOUND OF THE HEART WITH BENIGN MANIFESTATIONS

INVOLVEMENT OF THE DIAPHRAGMATIC SURFACE OF THE HEART WITH
PAIN REFERRED TO THE SHOULDER AND NECK

JACOB J. SILVERMAN, M.D.
STATEN ISLAND, N. Y.

WOUNDS of the heart produce a variable clinical picture, depending on their type, size, and location. Ordinarily, in wounds of the heart the signs and symptoms of cardiac tamponade are considered. The picture is dramatic and its prompt recognition has important therapeutic implications. Not all wounds of the heart, however, are accompanied by free bleeding into the pericardial cavity, nor are they necessarily serious or fatal. A wound of the heart, regardless of its severity, which involves one of the coronary arteries may result in a fatal hemorrhage or infarction. Also, a wound of one of the auricles is particularly liable to result in uncontrolled hemorrhage. The auricle is a thin-walled chamber and has relatively less power of contractility. On the other hand, the location of the wound may be such as to present an entirely asymptomatic clinical picture. The following case report is an example of a shrapnel wound of the diaphragmatic surface of the right ventricle, confirmed by operation. This wound was at first asymptomatic, but subsequently gave rise to pain in the left shoulder and neck, presumably a referred type of pain set up by the location of the shrapnel near the left dome of the diaphragm. The patient was carefully studied six months after the operation; he was found to be in excellent health and free of complaints.

CASE REPORT

The patient was a 32-year-old white staff sergeant, with over two years' military service. His past health had been excellent. On Oct. 1, 1944, while taking part in action during the campaign around Aachen, Germany, he was struck by a piece of shrapnel from enemy mortar fire, and sustained a penetrating wound of the right anterior chest wall at the fourth intercostal space. Antishock therapy was immediately instituted, and within twelve hours he was on the operating table of an evacuation hospital. The right pleural space was aspirated. This procedure was followed by débridement and closure of the right chest wall. An exploratory laparotomy was also

From the Cardiovascular Section, U. S. Army General Hospital, Camp Butner, N. C.
Received for publication May 4, 1946.

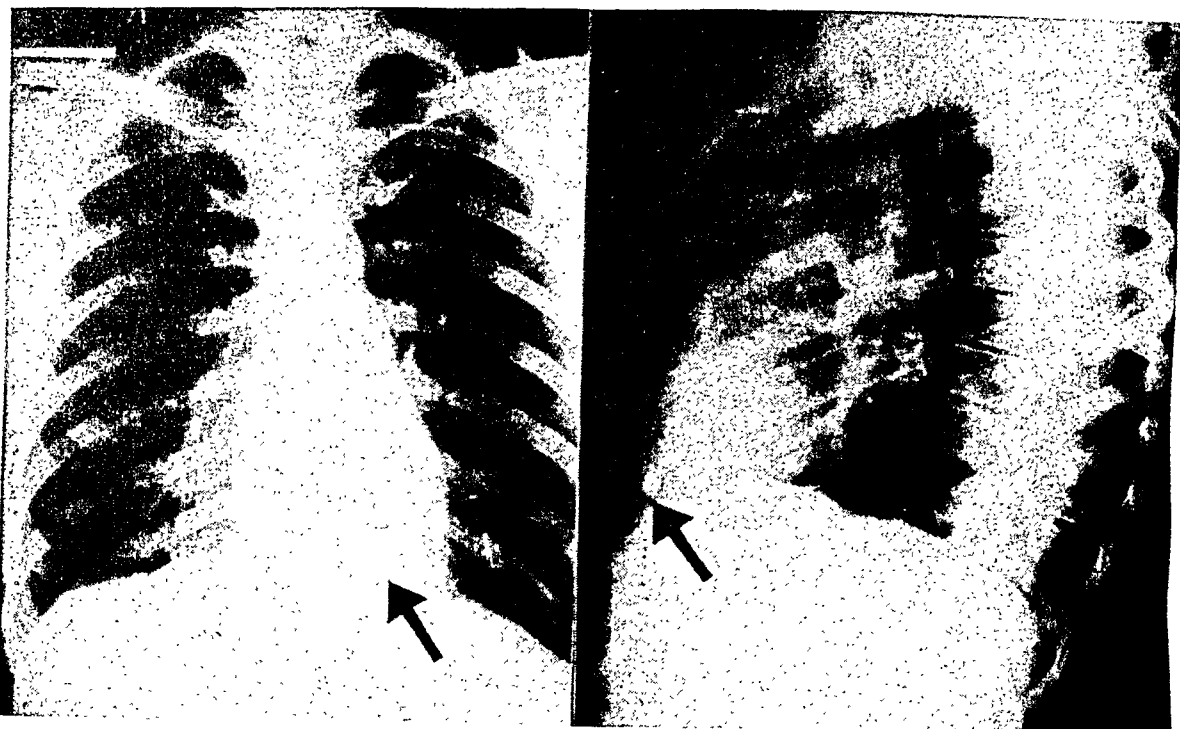


Fig. 1.—Preoperative roentgenograms of the chest demonstrating the piece of shrapnel lodged in the diaphragmatic surface of the heart.

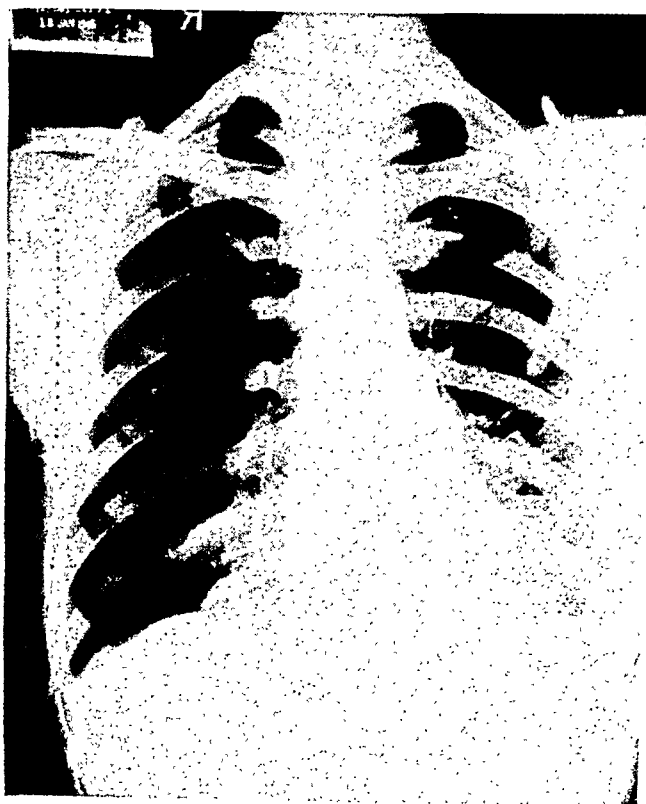


Fig. 2.—Postoperative roentgenograms of the chest taken three and one-half weeks after the removal of the piece of shrapnel shown in Fig. 3.

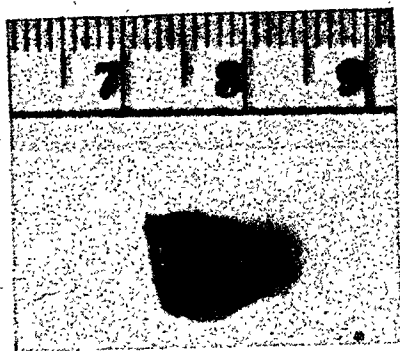


Fig. 3.—Photograph of the piece of shrapnel removed at operation from the right ventricle. The foreign body is approximately 7 x 7 x 8 millimeters.

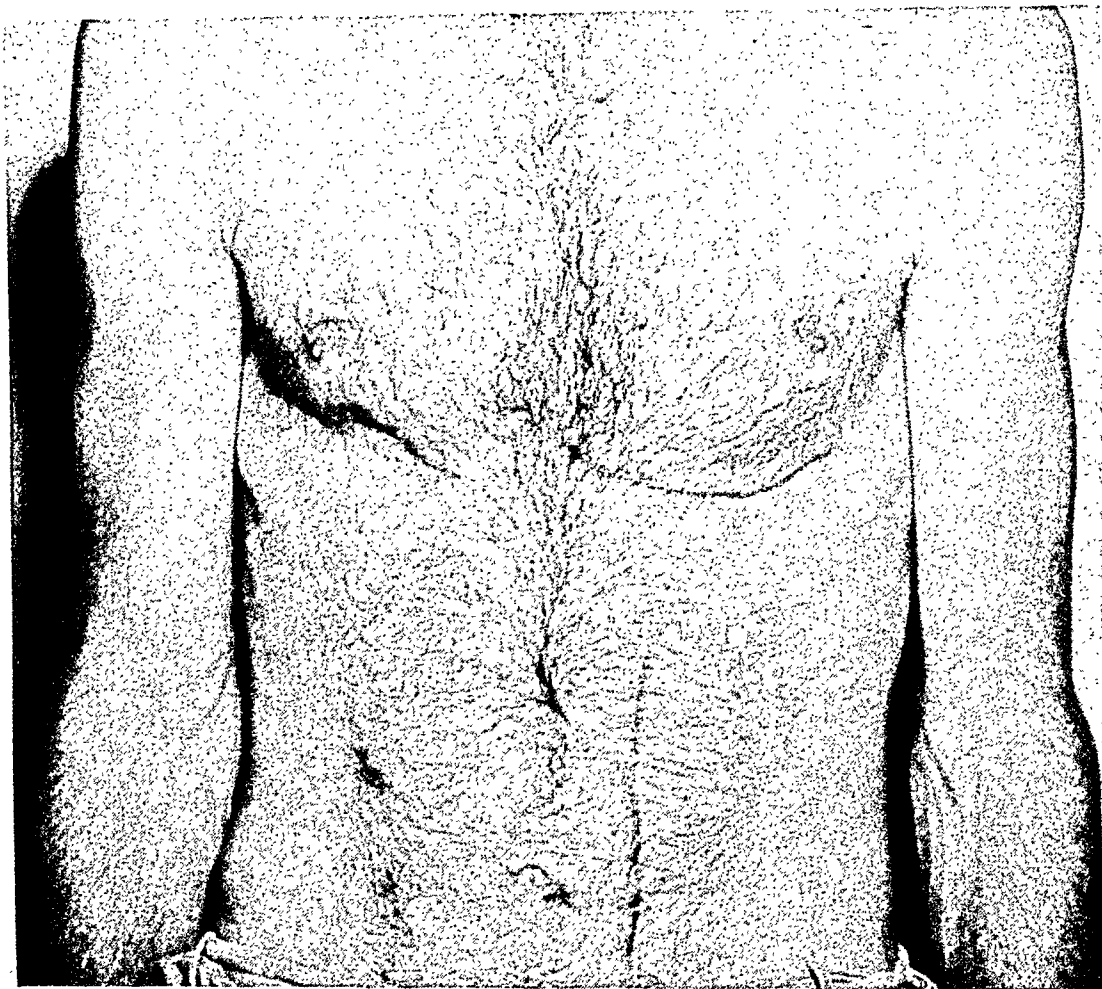


Fig. 4.—Photograph of patient taken six months after removal of the foreign body from the heart. The thinly visible scars have been outlined in pencil. The scar beneath the right nipple is the site of the original wound. The scar over the abdomen is from the exploratory laparotomy. The postoperative scar after removal of the foreign body is also shown on the left chest.

performed, but the findings were said to have been negative. The patient was then transferred through a chain of hospitals, and on Nov. 21, 1944, arrived at a general hospital in England. By this time, he was ambulatory and free of complaints. Preparations were in progress for his return to the United States. However, on Dec. 20, 1944, two and one-half months after the initial wound, he developed characteristic sharp pains in the left shoulder and neck, made worse by deep breathing. A fluoroscopic examination of the chest at that time revealed "a metallic foreign body in the region of the apex of the heart which moved with the cardiac pulsations." X-ray films taken in various positions confirmed the presence of a "metal foreign body measuring 7x8x8 mm., probably within the pericardial sac just above the diaphragm and just medial to the apex of the heart" (Fig. 1). On Dec. 26, 1944, an elective operation for the removal of the foreign body from the heart was undertaken. The operation was performed at the 140th General Hospital.*

General anesthesia was used and the following is the operative note taken from the records of the above hospital:

"The chest was opened through the fifth intercostal space anteriorly with division of the fifth and sixth cartilages close to the sternum. A segment of the sixth rib 1 cm. long, was removed laterally to facilitate exposure. The pericardium was opened laterally and readily separated from the myocardium. The foreign body was then felt just on the diaphragmatic side of the right ventricular wall 1.8 cm. medial to the anterior coronary artery running along the interventricular junction. Four silk traction sutures were placed and an incision made into the ventricular wall over the foreign body, which was removed. Moderate hemorrhage from the ventricle occurred. The myocardial wound was closed with two simple silk sutures and two traction sutures were tied over the suture line. The pericardium was closed with interrupted silk sutures except for a line 2 cm. long on the left side. The thoracic wall was closed in layers with interrupted sutures after 30,000 units of penicillin were placed in the pleural cavity. There was no significant change in pulse rate during the operation."

The patient made a remarkably prompt and uneventful convalescence (Fig. 2) and was evacuated to the United States on Feb. 26, 1945, exactly two months after the operation. It should be mentioned that the patient was entirely symptom free, but because of the unusual wound he was sent to a convalescent center, where he took part in the usual convalescent program, and at no time was he forced to limit his activities. In August, 1945, ten months from the time of the battle wound and six months after the operation, he was re-evaluated at the U. S. Army General Hospital, Camp Butner. An examination at this time revealed a sun-tanned, healthy appearing, well-adjusted soldier. When questioned about his operation, he quickly extracted from his pocket a small metallic foreign body and eagerly demonstrated "the piece of shrapnel removed from my heart" (Fig. 3). Physical examination from a cardiovascular standpoint revealed no significant findings. The operative wounds were well healed (Fig. 4) and unless looked for, the scars easily escaped detection. The apical impulse was normally localized in the fifth intercostal space inside the midclavicular line. There was good expansion of both lungs; the breath sounds were normal. The heart sounds were of good quality, regular, and no murmurs were heard. The rate was 80 per minute; the blood pressure was 125/80 in the right arm and 120/76 in the left arm. The peripheral vessels were normal. Routine laboratory studies, including urinalysis, blood count, and sedimentation test, were normal. On fluoroscopic examination the cardiac silhouette appeared normal. No abnormal pulsations were seen.

Detailed electrocardiographic studies were made (Fig. 5). Standard electrocardiograms (Leads I, II, and III) showed a slight widening of the QRS complex (.11 second). Extremity studies (V_R , V_L , and V_F) revealed a pattern seen in a semivertical type of heart.⁸ Precordial studies (Leads V_1 , V_2 , V_3 , V_4 , V_5 , and V_6) demonstrated a pattern seen in impairment of conduction of the right bundle branch.^{4,8} Application of the exploring electrode† over the ensiform region

*The operation was performed by Lt. Col. George N. J. Sommer, Jr., Medical Corps, Army of the United States, and the assistants were Lt. Col. Clyde W. Everett, Medical Corps, and Capt. Charles E. McCulloch, Medical Corps, Army of the United States. The anesthesia was administered by Capt. Phyllis Conley, Army Nursing Corps.

†In these studies the central terminal electrode technique was used.

(V_E) and over the right upper quadrant in the midclavicular line beneath the costal margin, *RUA*, revealed a characteristic, widened M-shaped type of QRS complex. An esophageal tracing, *E*, taken at the level of the ventricle (50 cm.) showed a Q wave of .3 to .4 mv., and a widened QRS complex. The Master two-step exercise test gave normal findings.

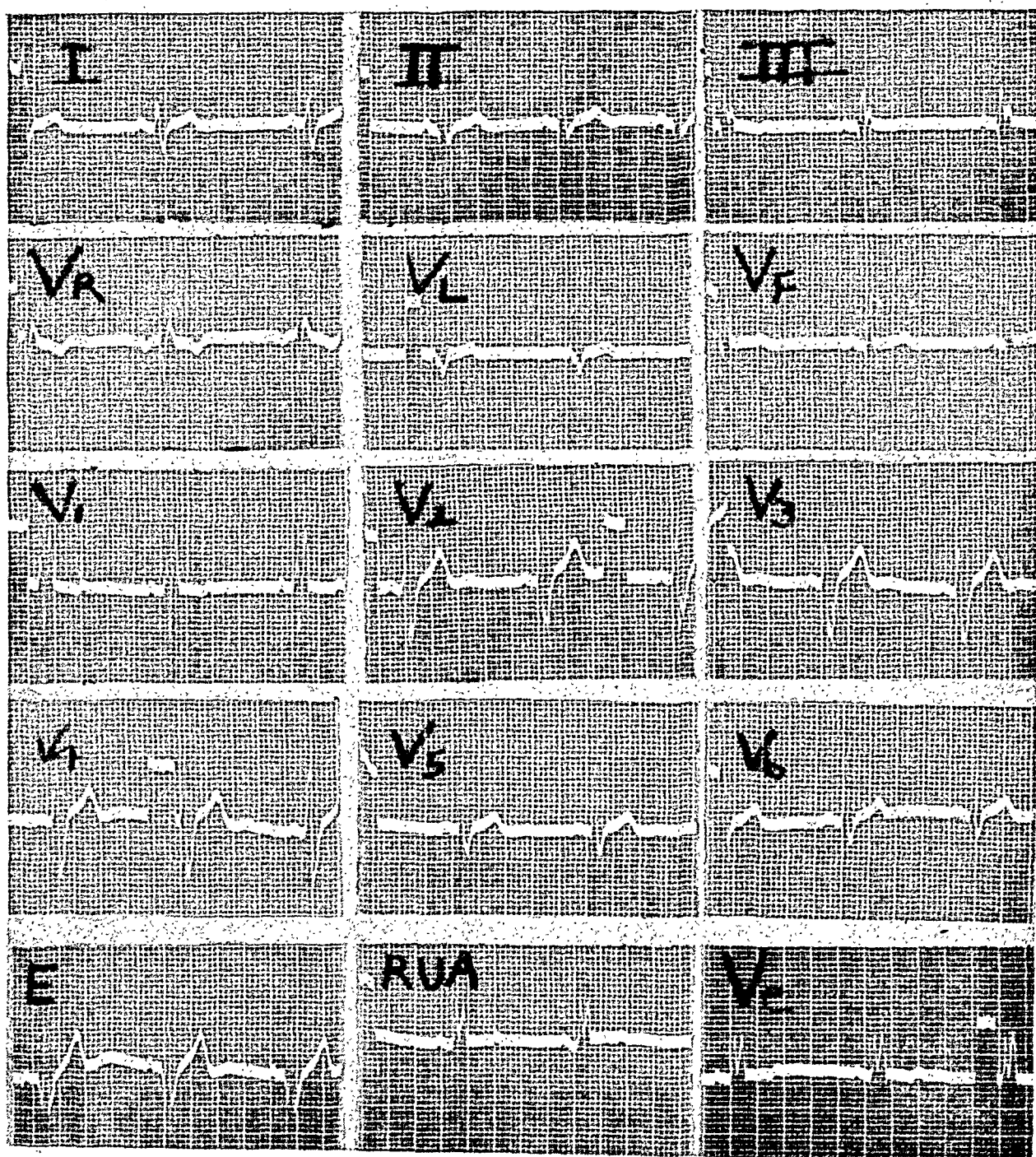


Fig. 5.—Upper row (Leads I, II, and III) shows the electrocardiograms of the three standard leads. The second row are extremity studies: right arm, (V_R); left arm, (V_L); and left foot, (V_F). The third and fourth rows are precordial studies. *E* is an esophageal tracing taken at the level of the ventricle (50 centimeters). Lead *RUA* was taken with the exploring electrode over the right upper quadrant in the midclavicular line beneath the costal margin. V_E is a tracing from the ensiform region. In these studies the central terminal electrode technique was used. For discussion, see text.

DISCUSSION

The symptomless feature of foreign bodies embedded in the heart is not new, and has been commented upon by others.^{3,5,7} The frequent incidental finding at autopsy of long existing foreign bodies in the heart clearly testifies that no symptoms need occur because of their presence. Experimentally, ordinary stimuli applied to the heart give rise to no painful sensation. The heart like the liver and the intestine, may be traumatized, cut, or burned without evidence of pain.¹ The classical reference to the insensitivity of the surface of the exposed heart was Harvey's demonstration of this phenomenon in the exposed heart of Viscount Montgomery.¹ Silverman and Cove⁶ reported a patient in which a bullet had been embedded in the heart musculature for forty-one years. This patient was asymptomatic and the bullet was localized by the roentgenkymograph.

Not all foreign bodies, however, are asymptomatic. Once implantation of a foreign body takes place, inflammatory changes may follow.³ These changes may act as foci of irritation to adjacent structures such as nerves, pleura, and diaphragm. In view of Capps' work,² the complaint of pain in the region of the left shoulder and left side of the neck in our patient is of experimental and clinical interest. The location of the shrapnel, accurately confirmed at operation, was unique. The piece of shrapnel entered the right chest, traversed the right lung and strategically lodged itself in the musculature of the diaphragmatic surface of the right ventricle adjoining the central portion of the diaphragm (Fig. 1). Capps² has shown that the sensory supply of the diaphragmatic pleura is derived from two sources, the phrenic nerve which innervates the central portion of the diaphragmatic pleura, and the last six intercostal nerves which innervate the outer portion of the diaphragmatic pleura. Experimental irritation of the central portion of the diaphragmatic pleura gave rise to a true referred pain in the corresponding neck and shoulder region, the impulses travelling by way of the phrenic nerve trunk to reach the third and fourth cervical spinal segments. It is interesting to note that our patient was free of symptoms until two and one-half months after the initial wound, at which time he developed the pains in his neck and left shoulder region, made worse by deep breathing. During this period, apparently, involvement of the diaphragmatic pleura was minimal. It is a well known clinical fact that changes involving the surface of the heart and pericardium may be extensive but unless the adjoining pleura is involved no appreciable pain may be experienced.²

Electrocardiograms taken on patients with wounds or foreign bodies embedded in the heart musculature may be perfectly normal. In this respect, not all myocardial infarcts produce changes in the electrocardiogram. The region involved cannot always be explored by the various positions of the electrodes. Furthermore, cardiac wounds are usually small and often little of the musculature is involved. Where there is severance of the conduction system, however, the changes are quickly and easily registered in the electrocardiogram.

The electrocardiographic tracings in our patient are interesting. There is little doubt that the electrocardiograms display abnormalities in both the chest and limb leads which are usually ascribed to right bundle branch block.^{4,8} With-

out a preoperative electrocardiogram for comparison, it is impossible to determine whether the shrapnel or the postoperative myocardial scar caused these changes, since such defects in conduction are encountered, at times, in young subjects who show no other symptoms or signs of organic disease.

SUMMARY

1. A case is presented of a soldier who had a shrapnel wound of the heart and was asymptomatic except for referred pain in the left shoulder and neck region.

2. The foreign body was accurately localized and successfully removed at operation. It consisted of a piece of shrapnel 7 x 7 x 8 mm. which was embedded in the musculature of the diaphragmatic surface of the right ventricle.

3. Foreign bodies of the heart may be asymptomatic and, unless adjacent structures such as the diaphragmatic pleura are involved, no symptoms need arise.

4. The patient was carefully studied less than a year after being wounded and six months after the operation. He was found to be in excellent health and, except for some interesting electrocardiographic changes, there was no objective evidence of cardiac impairment.

REFERENCES

1. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, Baltimore, 1943, Williams & Wilkins Company.
2. (a) Capps, J. A.: *An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum*, New York, 1932, The Macmillan Company.
(b) Capps, J. A.: Pain From the Pleura and Pericardium, *Research Publ., A. Nerv. & Ment. Dis.* 23:130, 1943.
3. Decker, H. R.: Foreign Bodies in the Heart and Pericardium. Should They be Removed? *J. Thoracic Surg.* 9:62, 1939.
4. (a) Goldberger, E.: An Interpretation of Axis Deviation and Ventricular Hypertrophy, *AM. HEART J.* 28:621, 1944.
(b) Goldberger, E.: The Differentiation of Normal from Abnormal Q waves, *AM. HEART J.* 30:391, 1945.
(c) Goldberger, E.: The Basic Electrocardiographic Patterns in Bundle Branch Block, *J. Lab. & Clin. Med.* 30:213, 1945.
5. King, E. S. J.: *Surgery of the Heart*, Baltimore, 1941, Williams & Wilkins Company.
6. Silverman, M., and Cove, A. M.: Intramyocardial Bullet Localized by Roentgenkymography: Report of a Case, *M. Ann. District of Columbia* 11:146, 1942.
7. White, P. D.: *Heart Disease*, ed. 3, New York, 1945, The Macmillan Company.
8. (a) Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
(b) Johnston, F. D., Rosenbaum, F. F., and Wilson, F. N.: The Ventricular Complex in Multiple Precordial Studies, Part I, *Mod. Concepts Cardiovasc. Disease* 12:6, 1943, American Heart Association, New York.
(c) Johnston, F. D., Rosenbaum, F. F., and Wilson, F. N.: Part II, *Mod. Concepts Cardiovasc. Disease* 12:7, 1943, American Heart Association, New York.

ASYMPTOMATIC CONGENITAL COMPLETE HEART BLOCK IN AN ARMY AIR FORCE PILOT

LIEUTENANT LOUIS B. TURNER
MEDICAL CORPS, ARMY OF THE UNITED STATES

CASES of congenital complete heart block have been reported in sufficient numbers to make the condition well known to the cardiologist, if not to the general practitioner. This case of heart block in an Army Air Force pilot is reported because it emphasizes in a striking way the benign course that such a disease may take, and suggests that, as in many other cardiac arrhythmias, the ultimate prognosis in heart block is dependent on the nature and the progressiveness of the underlying cardiac disease and not on the arrhythmia itself.

CASE REPORT

A 24-year-old Army Air Force bomber pilot was admitted to Mitchel Field Regional Station Hospital on May 26, 1946, for evaluation of a bradycardia discovered during a routine physical examination. He was entirely asymptomatic.

The patient was born Sept. 20, 1921, a normal infant as far as can be determined at this date. He was not cyanotic and required no resuscitation. At the age of 10 days he had a mild short-lived episode of respiratory distress, the nature of which cannot now be determined. As a child the patient had uncomplicated measles, mumps, and chicken-pox, and suffered no sequelae. At the age of 5 years he had a mild attack of pneumonia, also without known complications or sequelae. He had occasional sore throats, none of which were very severe. A tonsillectomy was performed at the age of 7 years. He never had any of the symptoms or signs of acute rheumatic fever, diphtheria, or scarlet fever. He denied having had any venereal disease. When 8 years of age, during a minor upper respiratory infection, he was examined by the family physician who told his mother that he had a slow pulse rate, but that it was normal for him and that he had always had it. Family history, as given by the patient, revealed no known cardiac anomalies or arrhythmias, and no known familial disease tendencies.

As a youth he indulged vigorously in all activities and sports without symptoms of any kind. He denied specifically ever having fainted or suffered a convulsive seizure, or ever having had chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, or palpitation.

He was inducted into the Army July 7, 1942. During his Army career he had numerous physical examinations, including many by the Flight Surgeon's office. His pulse was variously reported during this period as ranging between 48 and 80 resting, and 60 and 110 beats per minute after exercise. It was also stated that the heart rate always returned to the resting level within two minutes. On several occasions a systolic murmur was heard at the cardiac apex. This was always considered to be functional. He became a Flight Cadet in April, 1943, and went through the very strenuous physical training that this course entails. He recalled having covered a cross-country course with unbroken running over the period of an hour with less discomfort than most of his fellow trainees. He was trained as a four-motor pilot and was sent overseas in 1944, as

From the AAF Regional Station Hospital, Mitchel Field, N. Y.
Received for publication Oct. 2, 1946.

the co-pilot on a B-24 Liberator Bomber. He completed ten missions, flying over 20,000 feet at low oxygen tensions with no ill effect. On the last mission his plane was hit by flak over Munich and was forced down in Switzerland. At no time did he suffer any traumatic injury during his stay in the Army. On his return to the United States the bradycardia was again noted at Fort Devens and an electrocardiogram was taken. This revealed complete heart block with auriculo-ventricular dissociation. He was sent to Westover Field and then to Mitchel Field Regional Station Hospital for further evaluation.

Examination revealed a well-developed slender white man, 5 feet, 11 inches in height, weighing 155 pounds, who appeared neither acutely nor chronically ill. Head, eyes, ears, nose, and throat were all normal. There was no lymphadenopathy; the thyroid gland was barely palpable. The chest was asthenic and symmetrical. The lungs were clear to auscultation and percussion. Blood pressure was 110/60. Resting pulse rate was 40 per minute, regular, and of good quality; immediately after vigorous exercise, it rose to 72 per minute and was still regular. Two minutes after exercise it was again 40 per minute. The change between these rates was gradual. All peripheral pulses were normal. The strongest pulsations in the neck were observed to correspond with the peripheral arterial pulse. Although they could not be accurately counted, smaller, more frequent venous pulsations could be seen; sometimes superimposed on the arterial pulsations, sometimes irregularly spaced between the arterial pulsations. The apex beat was felt in the fifth intercostal space, 9 cm. from the midsternal line. There were no thrills or abnormal thrusts palpable. The heart sounds were of good quality, but the first heart sound at the apex seemed to vary in intensity from beat to beat. The second aortic sound was of the same quality as the second pulmonic sound. There was a Grade 2, blowing systolic murmur heard best within the apex, radiating medially and upward. This murmur was loudest when the patient was in the supine position. There was no diastolic or presystolic murmur, but irregularly, after every few heart beats during the diastolic phase, an extra heart sound could be heard. The abdomen was flat, nontender, and no organs were palpable. All superficial and deep reflexes were equal and active. The remainder of the physical examination was negative.

Laboratory examination revealed a normal red cell count of 4,950,000 erythrocytes, hemoglobin 94 per cent, and 7,400 white blood cells with a normal differential count. Sedimentation rate (Westergren) was 3 mm. in one hour. Urine was normal. The Kahn test was negative. The arm-to-tongue circulation time (calcium gluconate) was 12 seconds. Teleroentgenogram (Fig. 1) and cardiac fluoroscopy revealed no abnormality in size and shape of the heart. There was no individual cardiac chamber enlargement.

The electrocardiogram (Fig. 2) taken with patient at rest revealed complete auriculoventricular dissociation, with an auricular rate of 74 and a ventricular rate of 42 per minute. There was a slight auricular arrhythmia. The time between successive P waves was regularly shorter when a QRS complex comes between them than when there is no intervening QRS complex. (This auricular arrhythmia in heart block was most recently discussed by Parsonnet and Miller, 1944.) There were no axis deviation or abnormalities other than the dissociation.

The effects of exercise, full inspiration and full expiration, a hypodermic injection of 1 c.c. of 1:1,000 epinephrine hydrochloride, and of 1 mg. atropine sulphate were tried and recorded electrocardiographically. At no time was there a change in degree of heart block. Slight nervousness and palpitation were felt after the injection of adrenalin, but no other symptoms were noted. The exercise consisted of hopping in place for one minute. With the exception of exercise, the other procedures produced only a moderate effect on the auricular rate, and almost no effect on the ventricular rate. This is shown in Table I.

In view of the lack of history of rheumatic fever, diphtheria, syphilis, trauma, or other predisposing illness, and in view of the history of bradycardia during early childhood, the heart block in this case is probably congenital in origin and probably associated with an interventricular septal defect. The relatively normal pulse rates recorded in some of his past Army physical exami-

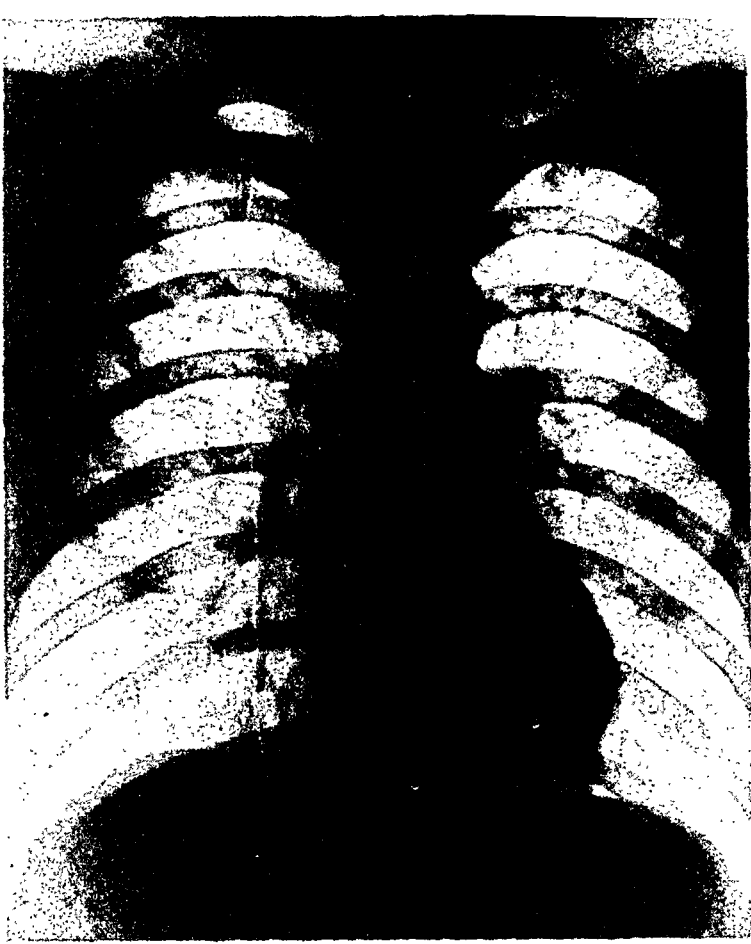


Fig. 1.—Teleroentgenogram of an Army Air Force pilot with asymptomatic congenital heart block.

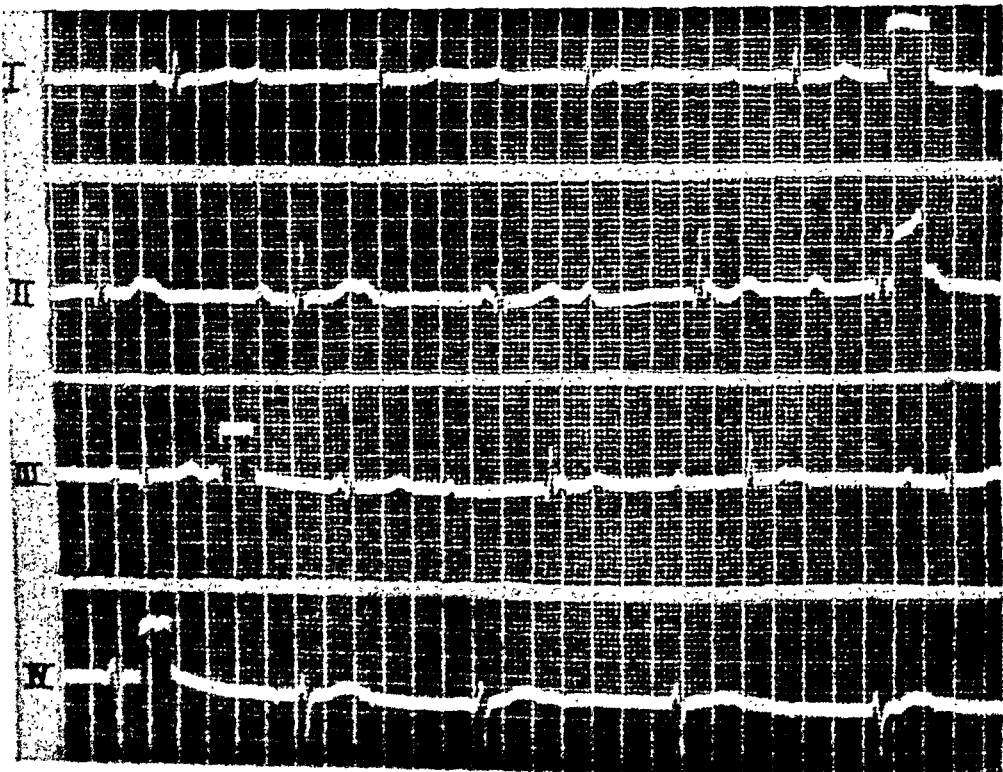


Fig. 2.—Electrocardiogram revealing the presence of complete A-V dissociation in an Army Air Force pilot.

TABLE I. THE EFFECT OF VARIOUS PROCEDURES ON THE AURICULAR AND VENTRICULAR RATES AS DETERMINED ELECTROCARDIOGRAPHICALLY

	AURICULAR RATE	VENTRICULAR RATE
Supine, at rest	62	40
Immediately after exercise	85	50
10 minutes after adrenalin	72	43
20 minutes after adrenalin	65	41
30 minutes after atropine	75	41

nations were probably the result of hurried examinations carried out in mass programs where pulse rates were frequently taken by enlisted men with little training.

DISCUSSION

Approximately 100 cases of congenital heart block have been recorded in the literature. The condition has been discovered and the diagnosis has been made most often during infancy and childhood. However, it has been diagnosed several times in utero² from the discovery of an otherwise unexplained fetal bradycardia; many times it has not been diagnosed until discovered for the first time during adulthood and middle age.

In a frequently quoted review, Yater³ in 1929 listed the following criteria as essential for the diagnosis of congenital heart block: (1) established block in a young person proven by graphic methods, (2) evidence of history of bradycardia at an early age, (3) absence of a history of any disease such as diphtheria, acute rheumatic fever, chorea, or syphilis which would be likely to leave permanent cardiac stigmata in a young person. He also listed as helpful in making a diagnosis two further criteria; (4) a history of syncopal attacks or convulsive seizures, and (5) presence of other signs of congenital heart disease, particularly of patent interventricular septum.

In addition to these criteria it should be mentioned that the ventricular rate is likely to be faster in congenital heart block where it usually ranges between 40 and 50 than it is in acquired heart block where it usually ranges between 30 and 40 per minute. Campbell⁴ points out that this relatively fast rate in congenital heart block frequently causes it to be overlooked in routine physical examinations. The relative frequency of congenital heart block as compared with acquired heart block is reflected in Campbell's statistics.⁵ He studied seventy-four cases of permanent complete heart block and concluded that ten cases, or 13 per cent, were congenital. He found also that eighty-four per cent of the cases of acquired heart block occurred after the age of 50 years. Thus, in the younger age groups at least half of the cases were presumably congenital in origin.

The possible etiology of congenital heart block has been discussed many times. However, the paucity of histologic material makes the discussion largely speculative. It is known that the most common associated congenital defect is a patent interventricular septum. In a case studied microscopically by Yater, Lyon, and McNabb,⁶ a defect in the interventricular septum was seen to com-

pletely separate the A-V node from the bundle of His. However, it is unlikely that this is frequently the cause of heart block because the conducting fibers embryologically develop before the septum and usually run posterior to the site of the ventricular defect.⁷ In addition, cases of heart block have been reported with intact ventricular septa, and cases of only partial block with complete absence of the septum. The histologic findings of Yater³ and of Yater, Leaman, and Cornell⁸ who found complete separation of the A-V node from the A-V bundle by the central fibrous body, and of Wilson and Grant⁹ and others who found areas of fibrosis, noninflammatory in character, which infiltrated and encroached on the conduction system, suggest that congenital heart block is usually the result of an inherent defect in the development of the conduction system occurring independently, though often in conjunction with other congenital defects.

The great majority of cases reported have not been free from cardiac symptoms or from the various stigmata of cardiac disease. For example, of the thirty cases reported by Yater, twenty-eight had varying degrees of cardiac enlargement with mild to severe degrees of cardiac disability, and fifteen of these cases had some degree of cyanosis.

However, there have been several cases reported in normal healthy adults. Jaleski and Morrison¹⁰ in 1943 reported two cases of congenital heart block in healthy adults. One of them, a 20-year-old woman, was always in good health, worked in a sedentary position, but did complain constantly of easy fatigue and weakness. The other patient, a 31-year-old woman, was well and had undergone two pregnancies with little difficulty, but two years after the second pregnancy, during a period of considerable strain, had several fainting episodes suggestive of Adams-Stokes seizures. Both patients had murmurs suggesting a patent interventricular septum. Roentgen-ray examination of their hearts showed them to be normal in size and shape.

Smith¹¹ in 1921 reported the case of a 21-year-old man with complete heart block who had episodes of fainting between the ages of 3 and 9 years. These had disappeared and the patient at the time of the report had no disability from strenuous athletic exercise. His heart was slightly enlarged. His pulse rate averaged 42 per minute but, interestingly enough, rose to 58 with a regular sinus rhythm during complete expiration; his ventricular rate rose to 64 after exercise and to 56 per minute after atropine.

Davis and Stecher¹² mention a case, described by Callandré, of a 21-year-old man who withstood strenuous exercise without discomfort. He had complete heart block except when he was at complete rest, at which time he developed a regular sinus rhythm with a P-R interval of less than 0.2 second.

Campbell⁴ in 1943 reported a very interesting group of seven cases of complete congenital heart block varying in age between 22 and 42 years. All were well and led active normal lives. Four of these cases were men, one on active duty in the Royal Air Force as a ground electrician though he actually "passed for flying duties." Of the three women all were well and asymptomatic. The oldest who was 42 years of age was doing housework on a farm; the other two led more sedentary lives, partly because of easy fatigability and partly because

their doctors discouraged more activity. Only one of these patients had a history of Adams-Stokes attacks. All had x-ray evidence of slight cardiac enlargement and had murmurs suggesting patent interventricular septa.

The patient presented in this report fulfills Yater's criteria for the diagnosis of congenital heart block. Because of the complete absence of any symptoms and his ability to withstand the rigors of Air Force training and high altitude combat missions as well as or even better than many of his fellows, he passed through three and one-half years of Army life and underwent many routine physical examinations before it was decided to investigate his bradycardia. The A-V dissociation in the electrocardiogram, the nature of the heart sounds, and the systolic murmur which suggested a patent interventricular septum were the only positive findings. There was no evidence at all of any impairment of cardiac efficiency.

Although there have been only a few cases of asymptomatic congenital heart block reported in adults, those that have been followed up have continued to do well and to lead normal lives without developing noteworthy symptoms or having minor disabilities progress. It is felt, therefore, that the ultimate prognosis in the case presented here, and in similar cases, is excellent. This patient was advised to try to forget that doctors had discovered something wrong with his heart and to continue to take a normal part in all activities. He was urged, however, to avoid exerting himself to the point of exhaustion.

SUMMARY

1. A case of complete congenital heart block occurring in an asymptomatic Air Force pilot which escaped discovery during three and one-half years of active service in the Army has been presented.

2. The incidence of congenital heart block, the incidence of symptom-free cases, and their ultimate prognosis has been discussed.

REFERENCES

1. Parsonnet, A. E., and Miller, R.: The Influence of Ventricular Systole Upon the Auricular Rhythm in Complete and in Incomplete Heart Block, *AM. HEART J.* 27:676, 1944.
2. Thomson, J.: Congenital Complete Block, *Arch. Dis. Childhood* 18:190, 1943.
3. Yater, W. M.: Congenital Heart Block—Review of the Literature, Report of a Case With Incomplete Heterotaxy; The Electrocardiogram in Dextrocardia, *Am. J. Dis. Child.* 38:112, 1929.
4. Campbell, M.: Congenital Complete Block, *Brit. Heart J.* 5:15, 1943.
5. Campbell, M.: Complete Block, *Brit. Heart J.* 6:69, 1944.
6. Yater, W. M., Lyon, J. A., and McNabb, P. E.: Congenital Heart Block—Review and Report of the Second Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, *J. A. M. A.* 100:1831, 1933.
7. Brown, J. W.: Congenital Heart Disease, London, 1939, John Bale, Sons & Curnow, Ltd.
8. Yater, W. M., Leaman, W. G., and Cornell, V. H.: Congenital Heart Block—Report of the Third Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, *J. A. M. A.* 102:1660, 1934.
9. Wilson, J. G., and Grant, A. T.: A Case of Congenital Malformation of the Heart in an Infant Associated with Partial Heart Block, *Heart* 12:295, 1925.
10. Jaleski, T. C., and Morrison, E. T.: Congenital Block, 2 Cases in Healthy Adults, *Am. J. M. Sc.* 206:440, 1943.
11. Smith, S. C.: High Grade Heart Block, *J. A. M. A.* 76:17, 1921.
12. Davis, H., and Stecher, R. M.: Congenital Heart Block—Report of Additional Case With Review of the Literature, *Am. J. Dis. Child.* 36:115, 1928.

OBSERVATIONS ON BERIBERI HEART DISEASE

SAMUEL EPSTEIN, M.D.*
BROOKLYN, N. Y.

THE modern classical concepts of beriberi heart disease, first defined by Wenckebach^{1,2} and later elucidated by Weiss and Wilkins,³ are now undergoing revision. Blankenhorn and associates^{4,5} have made important recent contributions to our knowledge of the condition. Although the application of their criteria makes earlier diagnosis possible, these authors point out that many fundamental questions still remain unanswered. Solution of these problems will enable really early recognition of the condition and the institution of therapy in the incipient stages of the cardiovascular disturbances associated with beriberi. Such information also will be of value in recognizing cardiovascular effects of thiamine deficiency superimposed on organic heart disease⁶ or complicating prolonged febrile disorders.⁷ Likewise, it has long been felt that many of the cardiovascular disturbances accompanying thyrotoxicosis may well be explained by inadequate thiamine supply in the face of the markedly increased demand necessitated by the hypermetabolism of this condition. Many of the basic physiologic disturbances are similar in both states. Revised criteria may well aid in this regard.

The traditional diagnostic signs of Aalsmeer and Wenckebach,⁸ later substantiated by Weiss⁹ and by Weiss and Wilkins,³ include abnormally rapid circulation, prominent right heart, "pistol shot" arterial phenomena, gallop rhythm, syncope or shock, and critical improvement after specific treatment. By the application of these criteria alone many cases will be overlooked. Blankenhorn's⁴ revision of the findings necessary for diagnosis include enlarged heart with normal (sinoauricular) rhythm, elevated venous pressure, peripheral neuritis or pellagra, nonspecific changes in the electrocardiogram, absence of other evident etiological factors, gross deficiency of diet for three months or more, improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi. By these criteria a great many more cases will be recognized. The omission from the diagnostic criteria of the three "traditional signs" of prominent right heart, "pistol shot" sounds, and acceleration of the circulation is a long step forward. The additional requirement of corroborative signs of nutritive failure (peripheral neuritis or pellagra) is significant.

It may well be that the criteria of Aalsmeer and Wenckebach apply to the more advanced cases, and that those of Blankenhorn apply to an earlier state;

From the Coney Island Hospital.

Received for publication July 13, 1946.

*Associate Visiting Physician, Coney Island Hospital and Harbor Hospital.

it is possible that biochemical analyses in the future will enable diagnoses in the incipient state of avitaminosis, even preceding the cardiovascular phenomena. It is in that direction that we must strive.

CASE REPORT

M. E., a white woman 53 years of age, entered the hospital for the first time on March 13, 1945, with a story of insomnia for ten years which was relieved at first by drinking six to eight bottles of beer. When after five years this became ineffective, she turned to whiskey and milk for a sleeping potion. For the past five or six years she had been subsisting on five or six jiggers of whiskey in milk daily. Vegetables, meat, and cereals had been completely excluded. Three months prior to admission she had had an attack of diarrhea, without melena or pus. She remained in the hospital three days before signing her release against advice. Physical examination revealed no cyanosis, dyspnea, or edema. A lemon-yellow tint of the skin was noted. The buccal mucous membranes were pale and the tongue was smooth and atrophic. Examination of the heart revealed the heart sounds to be of fair quality, with a short, soft systolic murmur audible at the apex. The rhythm was regular, with a rate of 120 per minute. The liver extended two fingerbreadths below the costal margin. The spleen was not palpable. Rectal and vaginal examinations were negative. The blood pressure was 160/50. The temperature was normal. Urinalysis was negative. Studies of the blood revealed a hemoglobin of 28 per cent, 1.85 million red blood cells per c.mm., and 8,200 white blood cells per cubic millimeter. The total serum proteins were 5.8 Gm. per cent; the albumin was 3.5 Gm. per cent, and the globulin 2.3 Gm. per cent. The blood Wassermann test was negative. The blood sugar was 101 mg. per cent and the urea nitrogen 8 mg. per cent. The hematocrit was 16 volumes per cent. The erythrocyte sedimentation rate was elevated. Tests for occult blood in the stools were negative. A chest plate revealed cardiac enlargement to the left and moderate congestive changes of both lung fields (Fig. 1).

The patient re-entered the hospital on March 24, 1946, because of extreme weakness, shortness of breath, and swelling of the ankles, all of ten days' duration. She gave a history of having consulted a physician five years previously for weakness which had then been attributed to anemia. Since that time her teeth had been in poor condition, she had been unable to eat properly, and had subsisted on milk and alcohol with a resultant weight loss of 20 pounds. The anemic state had remained untreated.

Physical examination revealed marked dyspnea, evidences of weight loss, lemon-yellow sclerae, and marked conjunctival pallor. There were no petechiae. The tongue was pale and extremely smooth, the papillae were atrophic; fissures were present at the angles of the mouth. The neck veins were distended, but revealed normal systolic collapse. Bilateral basal moist râles were audible and the breath sounds were diminished at the right base. The cardiac apex was palpable in the fifth intercostal space beyond the midclavicular line. The rhythm was regular at a rate of 120 per minute. The palpable and audible phenomena of gallop rhythm were noted to the left of the sternum. There was a soft systolic murmur over the precordium. The second aortic and second pulmonic sounds were of equal intensity. Abdominal palpation revealed hepatic enlargement to the umbilicus; the spleen was palpable one fingerbreadth below the costal margin. Marked sacral and pretibial edema were evident. The deep reflexes were normal and position sense was intact. There was neuritic tenderness in both calves.

A summary of the laboratory data is given. The blood studies are shown in Table I, and the bone marrow studies in Table II. The hematological interpretation was that the marrow findings of April 8, 1946, were consistent with hyperchromic macrocytic anemia; on May 8, 1946, the findings were comparatively normal. Nutritional defects with deficiency of the extrinsic factor of Castle may have been causative.

On March 26, 1946, the total proteins were 6.0 Gm. per 100 c.c.; the albumin was 3.5 Gm. and the globulin 2.5 grams. The blood cholesterol was 126 mg. per cent and the cholesterol esters 62 mg. per cent. The blood glucose was 115 mg. per cent and the urea nitrogen 15 mg. per cent. The icterus index was 5 units and the thymol turbidity test of Maglacen was 7 units



Fig. 1.—March 15, 1945. Teleroentgenogram showing moderate cardiac enlargement and pulmonary congestion.

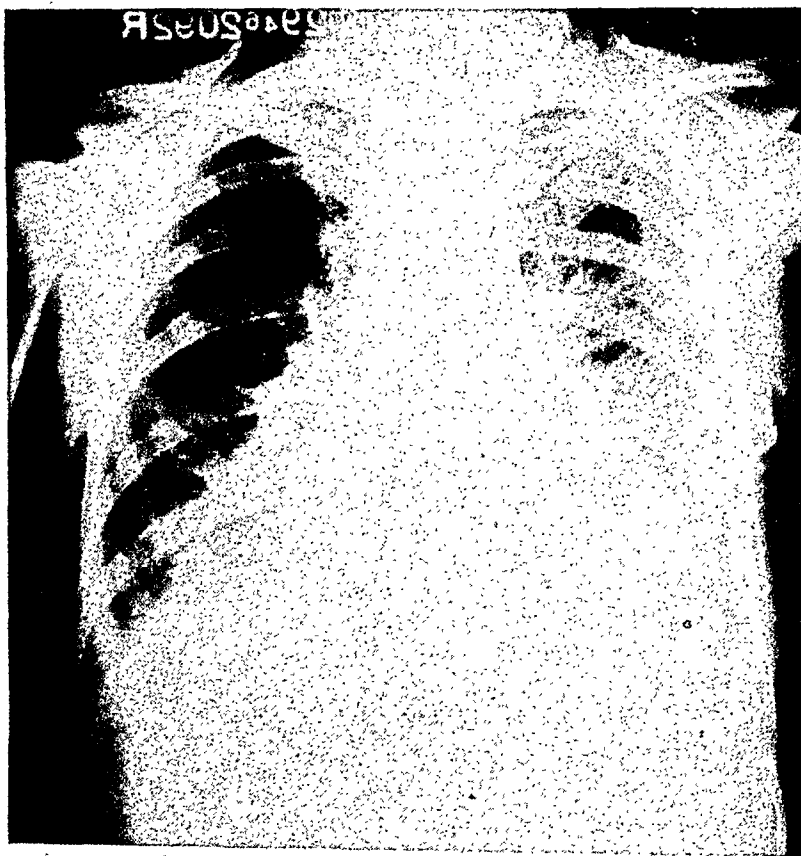


Fig. 2.—March 29, 1946. Teleroentgenogram showing marked cardiac enlargement and pulmonary congestion prior to sufficient specific therapy.

TABLE II.

	ON 4/8/46 (PER CENT)	ON 5/8/46 (PER CENT)
Myeloblasts	4	2
Myelocytes	8	19
Meta myelocytes	21	44
Polymorphonuclear leucocytes	23	14
Megaloblasts	11	0
Normoblasts	33	9
Erythroblasts	0	12

(normal to 4). The alkaline phosphatase was 3.3 Bodansky units. The prothrombin time was 6 minutes (Howell). The blood Wassermann test was negative. Hemolysis of the erythrocytes began at 0.46 per cent, and was complete at 0.36 per cent. The galactose tolerance test was normal. Urinalysis, including the test for Bence-Jones protein, was negative. Examination of the stools for occult blood was negative.

Gastric analysis with histamine revealed no free hydrochloric acid; the total acidity was 8.0, 13.4, 10.0, 13.4, and 11.0 in the fasting specimen, at 15 minutes, 30 minutes, 45 minutes, and one hour, respectively.

Roentgen-ray studies revealed calcification of the arteries of the legs, forearms, and pelvis. There was nonspecific rarefaction of the bones of the legs and osteoporosis of the left humerus. The skull was negative. Flat plate of the abdomen and detailed gastrointestinal studies revealed no abnormalities. On March 29, 1946, chest films revealed the heart to be enlarged in all diameters; there was bilateral pulmonary congestion and a small amount of fluid at both costophrenic angles (Fig. 2).

The rectal temperature was 100.5°F. during the first three days and then remained normal. The blood pressure readings were 140/50 (on admission) and then 114/62, 120/62, 124/66, 140/86, and 136/80. The weight increased from 87 to 89 pounds.

An electrocardiogram made on March 27, 1946, showed a P-R interval of 0.16 second, QRS duration of 0.08 second, and a heart rate of 108 per minute. All complexes were of low voltage. T₁ was isoelectric; T₂ and T₃ were positive but of low voltage (Fig. 3,A). On April 25, 1946, (Fig. 3,B) the tracing was normal. The T waves were upright in all leads, the P-R interval was 0.18 second and the QRS duration was 0.06 second.

On April 8, 1946, the venous pressure was 15 cm. of water and the arm-to-tongue circulation time (decholin), 12 seconds. On April 29, 1946, the venous pressure was 10 cm. of water and the arm-to-tongue time, 8 seconds.

On the following therapy, improvement was rapid so that by April 8, 1946, evidences of congestive failure had subsided in great part. Cervical vein distention was no longer present and only slight sacral edema persisted. By May 25, 1946, neither the liver nor spleen was palpable, no edema was present, and the patient was then discharged, greatly improved.

Therapy consisted of the daily oral administration of thiamine chloride, 100 mg., niacin, 150 mg., vitamin C, 200 mg., and vitamin A and D concentrate tablets. Blood transfusions of 500 c.c. were given on March 25, March 30, and April 9, 1946. A full diet was given as soon as it could be tolerated. Liver extract parenterally was not begun until April 10, 1946 by which time all signs of failure had disappeared.

On July 10, 1946, six weeks after discharge, the patient's weight had increased from 89 to 106 pounds. She had been on a full balanced diet with vitamin supplements. All alcoholic beverages were interdicted. Her functional capacity was excellent (she could walk two miles) and she was symptom-free.

Physical examination revealed no residual signs of vitamin deficiency. There was no dyspnea, cyanosis, edema, or venous congestion. The liver and spleen were not palpable. The heart

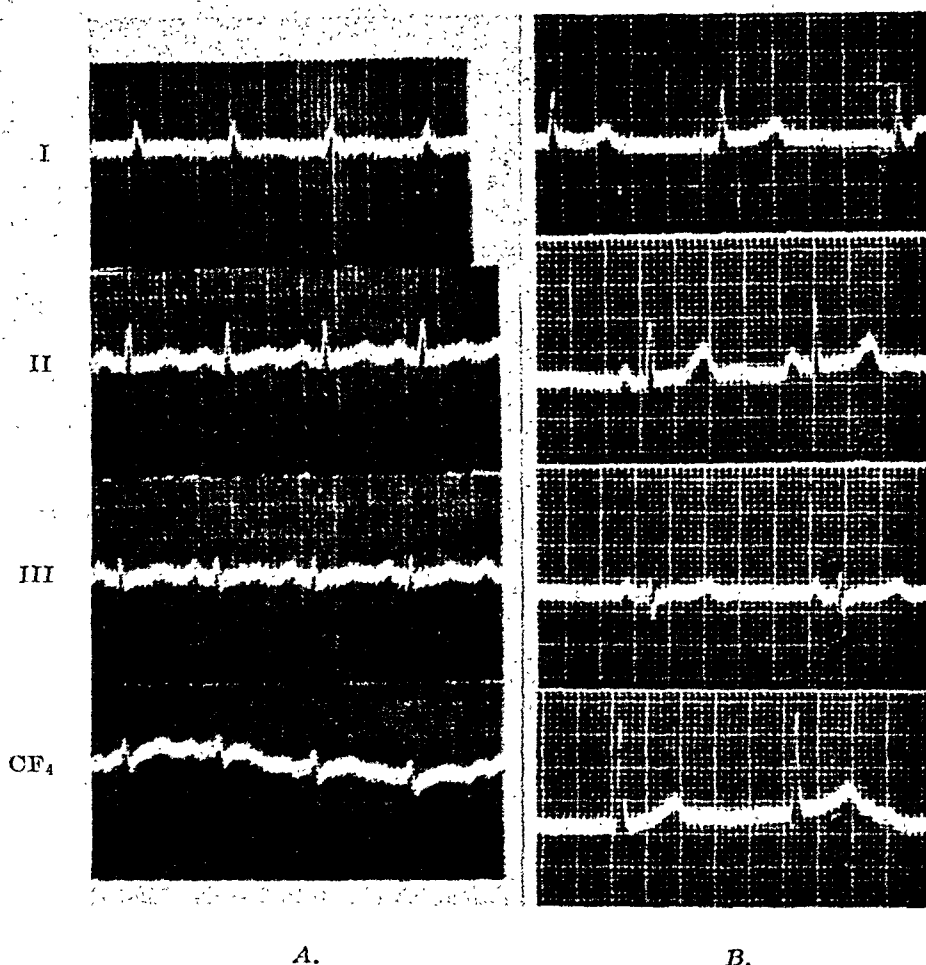


Fig. 3.—A, March 27, 1946. Electrocardiogram revealing low voltage of QRS complexes and flattening of the T waves before specific therapy. B, April 26, 1946. Normal electrocardiogram following specific therapy.

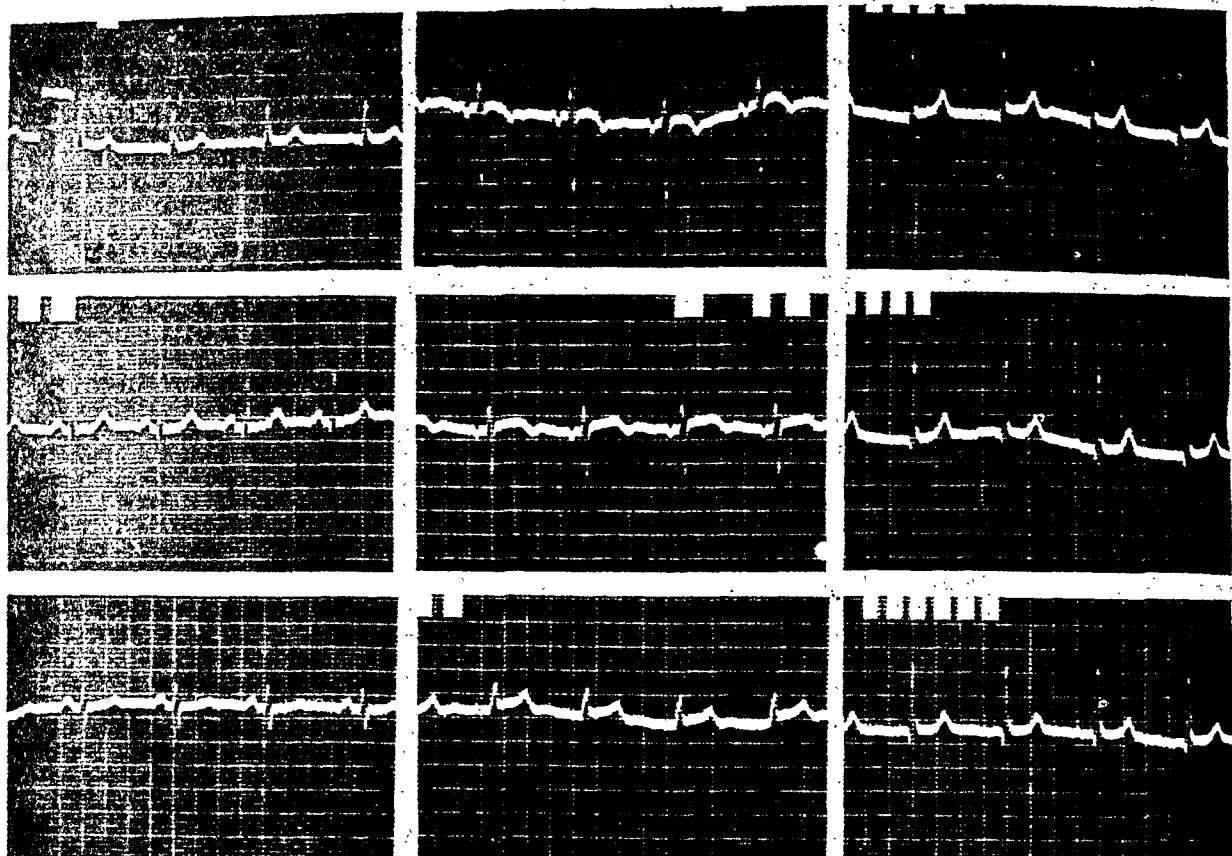
rate was 84 per minute and there was a regular sinus rhythm. A soft systolic murmur was audible over the precordium.

Electrocardiographic study revealed no significant changes in the comparable leads (Fig. 4). A teleroentgenogram revealed that the heart size still remained small and that there was no pulmonary congestion (Fig. 5).

It should be noted that on the first admission with severe anemia and minimal signs of failure, the heart size (Fig. 1) was not so great as, on the readmission with the same degree of anemia and severe congestive failure (Fig. 2). Follow-up study (Fig. 5) revealed striking decrease in the heart size.

COMMENT

This case presents many of the outstanding features of cardiovascular manifestations of thiamine deficiency. It is interesting that the severe anemia, as well as signs of avitaminosis, were present on the first admission without signs of frank congestive heart failure. Yet on the second admission the patient was in advanced congestive failure with very little advance in her anemia. The role of anemia in congestive heart failure is well known;¹⁰ the pathologic physiology of the circulation has been amply studied,¹¹ and roentgenographic changes of the heart in anemia have been described^{12,13} with reversal of the heart size



I, II, III

a_{VR} , a_{VL} , a_{VF}

V_1 , V_2 , V_3

Fig. 4.—July 10, 1946. Follow-up electrocardiogram remains within normal limits six and one-half weeks after discharge from hospital.

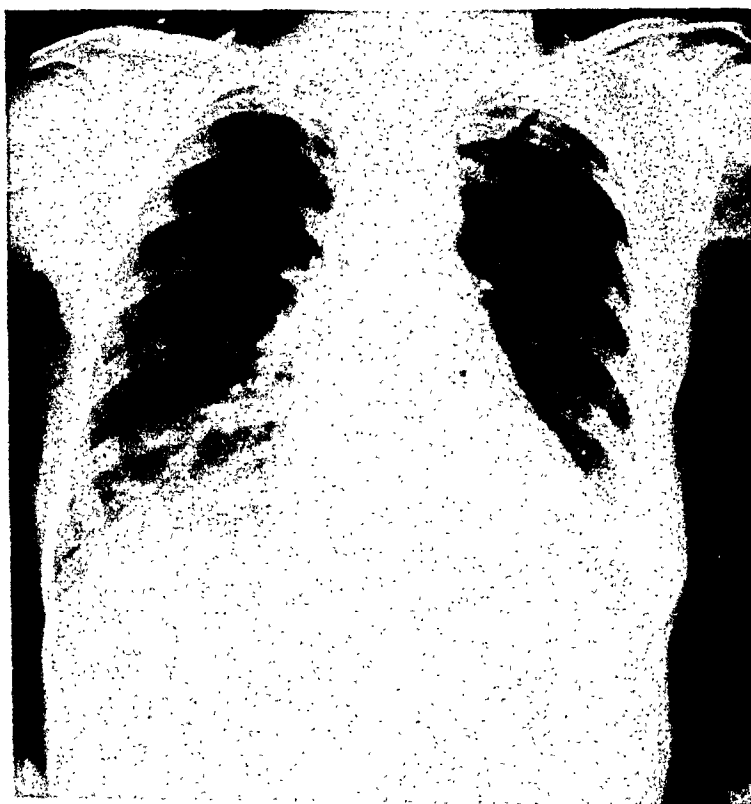


Fig. 5.—July 10, 1946. Follow-up teleroentgenogram reveals smaller heart size and absence of pulmonary congestion six and one-half weeks after discharge from hospital.

after correction of the anemia. The varied effects of acute anemia (hemorrhage, etc.) versus chronic anemia on the cardiovascular mechanism need no repetition.

In our case the prolonged inadequate diet, the physical findings of dietary deficiency, the enlarged heart with sinus rhythm, the dependent edema, the elevated venous pressure with comparatively rapid circulation time, the high pulse pressure on admission, coupled with the return of the electrocardiogram to normal, the reversal of cardiac enlargement, and the disappearance of signs of failure on specific therapy all support the presence of beriberi heart disease.

Obviously the severe anemia and probably arteriosclerosis were additional factors. The rapid response to vitamin therapy, even before the hematological response, is worth noting. Digitalis and the mercurial diuretics were not exhibited. The subsequent well-being of the patient with good functional capacity on a satisfactory dietary regime with vitamin supplements is significant.

It is well to point out the importance of precipitating causes such as infection and exertion superimposed on pre-existing vitamin deficiencies¹⁴ which might by themselves be insufficient to cause cardiac symptoms. The rectal temperature of 100.5° F. in our case does not necessarily suggest infection; it may be attributed to congestive failure alone.^{3,15a,15b,15c}

DISCUSSION

The reversible enlargement of the heart as seen in beriberi also occurs in myxedema, arteriovenous aneurysm, anemia, and following desoxycorticosterone overdose and withdrawal.¹⁶ In the latter work¹⁶ an attempt was made to show the basic physiologic similarities in desoxycorticosterone overdosage and thiamine deficiency.

The reversal of the electrocardiographic changes is well known in beriberi heart disease.^{17,18} Prolongation of the Q-T interval occurs here as well as in hypoparathyroidism, Addison's disease, uremia, and in such conditions as rheumatic carditis and cardiac infarction.^{17,18} The typical changes have been induced by diets deficient in thiamine and returned to normal on thiamine administration.¹⁹ T waves may become temporarily inverted at the start of specific therapy with vitamin B₁ and might be mistaken for coronary disease.^{3,20,21} Heart failure has recently been induced by producing experimental beriberi.²²

Observations related to circulatory disturbances in beriberi have shown increased cardiac output, elevated venous pressure, and accelerated speed of circulation.^{3,23} In the light of Blankenhorn and associates'^{4,5} data, it is likely that earlier stages of deficiency will yield other data.

SUMMARY

1. The recent diagnostic advances in the cardiovascular manifestations of beriberi have been emphasized.
2. The importance of superimposed etiological factors such as anemia, infection, exertion, have been stressed.
3. A typical case of avitaminosis with associated severe anemia and cardiovascular disturbances of thiamine deficiency has been presented.

REFERENCES

1. Wenckebach, K. F.: The Riddle of Beriberi Heart in Libman Anniv., 3:1199, 1932, International Press, New York.
2. Wenckebach, K. F.: Das Beriberi Herz: Morphologie, Klinik, Pathogenese, Berlin, 1934, Springer-Verlag.
3. Weiss, S., and Wilkins, R. W.: The Nature of Cardiovascular Disturbances in Nutritional Deficiency States, Ann. Int. Med. 11:104, 1937.
4. Blankenhorn, M. A.: The Diagnosis of Beriberi Heart Disease, Ann. Int. Med. 23:398, 1945.
5. Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S.: Occidental Beriberi Heart Disease, J. A. M. A. 131:717, 1946.
6. Warshawsky, H., and Weissberg, J.: Beriberi as a Complication of Organic Heart Disease, M. Bull. Vet. Admin. 20:287, 1944.
7. Perez, J. F. R.: Hypovitaminosis B₁ and Cardiovascular Disorders, Rev. de med. y cir. Habana 49:317, 1944.
8. Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beriberi Krankheit, Wien. Arch. f. inn. Med. 16:193, 1929.
9. Weiss, S.: Occidental Beriberi With Cardiovascular Manifestations, J. A. M. A. 115:832, 1940.
10. Bartels, E. C.: Anemia as the Cause of Severe Congestive Heart Failure: Report of a Case, Ann. Int. Med. 11:400, 1937.
11. Fahr, G., and Ronzone, E.: Circulatory Compensation for Deficient Oxygen-Carrying Capacity of the Blood in Severe Anemias, Arch. Int. Med. 29:331, 1922.
12. Ball, D.: Change in the Size of the Heart in Severe Anemia: With Report of a Case, AM. HEART J. 6:517, 1931.
13. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, 1943, Charles C Thomas, Publisher, p. 203.
14. Schott A.: Circulatory Failure Due to Vitamin B Deficiency, Brit. Heart J. 6:27, 1944.
15. (a) Cohn, A. E., and Steele, J. M.: Unexplained Fever in Heart Failure, J. Clin. Investigation 13:853, 1934.
(b) Steele, J. M.: Fever in Heart Failure, J. Clin. Investigation 13:869, 1934.
(c) Steele, J. M.: Elevation of Rectal Temperature Following Mechanical Obstruction to the Peripheral Circulation, AM. HEART J. 13:542, 1937.
16. Dassen, R.: Cardiac Enlargement and Desoxycorticosterone: Cardiac Pseudo-Beriberi, Medicamentous and Dietetic, Rev. Asoc. méd. argent. 56:643, 1942.
17. Dressler, W.: Clinical Cardiology, New York, 1942, Paul B. Hoeber, Inc., p. 568.
18. Katz, L. N.: Electrocardiography: Including an Atlas of Electrocardiograms, Philadelphia, 1941, Lea & Febiger, p. 283.
19. Williams, R. D., Mason, H. L., and Smith, B. F.: Induced Vitamin B₁ Deficiency in Human Subjects, Proc. Staff Meet, Mayo Clin. 14:787, 1939.
20. Campbell, S. B. B., and Allison, R. S.: Pellagra, Polyneuritis, and Beriberi Heart, Lancet 1:738, 1940.
21. Dustin, C. C., Weyler, H., and Roberts, C. P.: Electrocardiographic Changes in Vitamin B₁ Deficiency, New England J. Med. 220:15, 1939.
22. Keys, A.: Bi-Monthly Progress Report No. 20, Contract No. OEMcmr-27, Nov. 1, 1944, restricted.
23. Porter, R. R., and Downs, R. S.: Some Physiological Observations on the Circulation During Recovery From Vitamin B₁ Deficiency, Ann. Int. Med. 17:645, 1942.

CORONARY ARTERITIS WITH FATAL THROMBOSIS DUE TO SALMONELLA CHOLERAESUIS VARIETY KUNZENDORF

ROY N. BARNETT, M.D.,* AND S. L. ZIMMERMAN, M.D.†
COLUMBIA, S. C.

THE subject of *Salmonella* infection has been comprehensively reviewed by Bornstein¹ and the following remarks are based on his report. *Salmonella* infections may be divided into three clinical forms; *Salmonella* fever, *Salmonella* septicemia, and *Salmonella* gastroenteritis. There is some overlapping with changes from one form to another. It is only possible in a general way to correlate the species of invader with the type of clinical disease. Nevertheless, it is apparent that *S. choleraesuis*† is a virulent pathogen in man and is more likely to cause septicemia and death than any of the other common *Salmonella*. In the tabulated records of 500 human *Salmonella* infections from the N. Y. *Salmonella* Center, fifty-five were caused by *S. choleraesuis*; of these fifty-five, twenty-one were instances of septicemia and nine (16 per cent) were fatal. *Salmonella* has been reported as a cause of endocarditis, meningitis, osteomyelitis, and abscesses in many parts of the body. There have been few specific correlations between the observed human pathology and the implicated *Salmonella* species. In general, the infection may be associated with no lesions, with typhoidlike lesions, or with lesions similar to those produced by the pyogenic cocci. When no lesions are present, death is attributed to toxemia. In the experimental lesions produced in the mouse by intra-abdominal injections of *S. typhimurium*, either living organisms or antigenic extracts, there are found mononuclear infiltrations of the adrenal medulla with parenchymal degeneration, focal necroses in the liver, follicles of the spleen and lymph nodes, and congestion of the portal vessels with or without thrombosis and hemorrhage. The latter lesions may have some bearing on the case to be presented.

Salmonella choleraesuis is more sensitive to the sulfonamides, particularly sulfaguanidine, than most other *Salmonella* organisms. Administration of sulfonamides in disease caused by this species is recommended.

CASE REPORT

W. Q. A., a 48-year-old white man, was admitted to this hospital on March 24, 1945, complaining of a discharge from the right ear which had begun fourteen days previously, one week after a cold. He had been given twenty-four tablets of a sulfonamide preparation. During the

Published with the consent of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed by the authors. Received for publication April 26, 1946.

*Pathologist, Veterans Administration Hospital.

†Chief of Medical Service, Veterans Administration Hospital.

‡This organism is referred to in the older literature as *S. suipestifer*. The variety Kunzendorf is the so-called "European" strain, differing from the "American" strain in hydrogen sulphide production and certain other cultural reactions.

administration of this drug he noticed pain in the legs and right arm with slight swelling of the right wrist. Three to four days before admission he noted chills and fever. The history otherwise was irrelevant.

Physical examination on admission revealed a thin man who did not appear acutely ill. The temperature was 100° F., and the pulse rate 100 per minute. The right ear drum was perforated and there was a purulent discharge in the external auditory canal. There was slight tenderness over the tip of the right mastoid but no swelling. The throat was congested. The blood pressure was 130/80. The heart and lungs appeared normal. There was no splenomegaly, lymphadenopathy, skin rash, or petechiae. Neurological examination was entirely negative. There was tenderness of both calves and the right wrist with no obvious swelling. The white blood count was 11,600, the differential count was normal, the red blood count was 4.25 million, and hemoglobin was 86 per cent (13.9 grams, photoelectric). The blood serology was negative. The urine was normal. The diagnosis on admission was acute purulent otitis media with probable mastoiditis.

An x-ray film of the mastoid sinuses was negative. The ear continued to drain moderately, but the patient had no pain. The consulting otologist did not believe that a mastoiditis was present. Sulfadiazine therapy was instituted on March 26, and on March 27 the blood level was 4.4 mg. per 100 cubic centimeters. The drug, however, was discontinued after only 3 Gm. were taken because of its possible etiological role in the production of the arthralgia. At this time the presence of acute rheumatic fever was considered likely and the patient was given salicylate therapy, receiving 1,080 grains by rectum in six days. The temperature ranged between 100 and 103.8° Fahrenheit. An x-ray film of the chest was negative. On April 1, a small macular hemorrhage was seen in the right ocular fundus. It was associated with blindness of this eye, which persisted until death. On April 2, a purpuric spot appeared on the left palm. It was believed then that the patient was exhibiting a late reaction to the sulfonamides, manifested by arthralgia, fever (which reached 106° F. on April 4), and a probable thrombocytopenia. The platelet count, however, was 550,000, and the white cell count reached 19,600, with 86 per cent polymorphonuclear leucocytes. Salicylates were discontinued on April 1. On April 3, another hemorrhage was seen in the right fundus and paresis of the right upper extremity occurred. The neck remained supple. A mitral systolic murmur was heard on this date and the possibility of septicemia or brain abscess was considered. Spinal tap revealed an initial pressure of 150 mm. of water, a clear fluid, and normal manometrics. A cell count and the protein and dextrose content of the fluid were normal.

A blood culture was made on April 3, and reported as negative. The patient was given penicillin therapy, however, because of his critical febrile condition despite the fact that no organisms had as yet been isolated. Purpuric eruptions now appeared on both palms. The spleen was not palpable. There were no petechiae. The neurological findings remained unchanged. It was felt that the apical systolic murmur was of no diagnostic significance. The patient remained alert mentally. On April 5, the right pupil was found to be fixed while the left reacted sluggishly. On this date the blood culture of April 3 was reported positive for an unidentified gram-negative rod. The urine culture was positive for the same organism. The Widal and Brucella agglutination tests were negative. The intradermal skin tests for brucellosis were also negative.

A culture was sent to the University of Kentucky Agricultural Experimental Station and was later reported by Dr. Phillip Edwards as *Salmonella choleraesuis*, variety Kunzendorf. In the interim, in vitro studies with reference to penicillin sensitivity of the organism revealed that it grew luxuriously in a medium containing 25 units of penicillin per cubic centimeter. With this information at hand, and because no apparent improvement had followed administration of the drug, penicillin therapy was discontinued after the patient had received 1,620,000 units. The paresis of the right arm improved and soon disappeared but the right eye remained blind.

Endocarditis due to *Salmonella* appeared to be the most likely diagnosis at this time. The patient continued to have fever, although at a lower level. The apical systolic murmur remained unchanged and there was some improvement in the general condition. At 8:30 A.M., on April 24 the patient was found to be in shock with marked venous congestion of the neck and head. The heart sounds were poor. The blood pressure could not be recorded. An electrocardiogram

revealed an acute anterior wall infarction (Fig. 1). A gallop rhythm was present and Cheyne-Stokes respirations soon ensued. The patient expired at 3:35 P.M. the same day.

The final clinical diagnoses were:

1. Sepsis, due to *Salmonella choleraesuis*, variety Kunzendorf.
2. Heart disease of unknown etiology, probably bacterial embolization, with coronary occlusion and myocardial infarction.
3. Embolic closure, right retinal vessels and possibly the left lenticulostriate artery, with right hemiparesis.

Autopsy.—The heart weighed 350 grams. The valves and chambers were normal. The coronary arteries were thin-walled and widely patent, except for a gray, soft, slightly adherent occlusive thrombus in the left anterior descending artery about 2 cm. from the aortic ostium, measuring about 1 cm. in length. The myocardium of the anterior wall of the left ventricle was mottled dark red and yellow, contrasting with the red-brown normal muscle elsewhere.

The spleen weighed 350 grams. It was soft and red, with prominent corpuscles. There was an abscess at the lower pole containing about 10 c.c. of thick yellow pus from which *S. choleraesuis* organisms were cultured.

The colon exhibited mucosal hemorrhages in its ascending portion for a distance of about 15 cm. above the cecum.

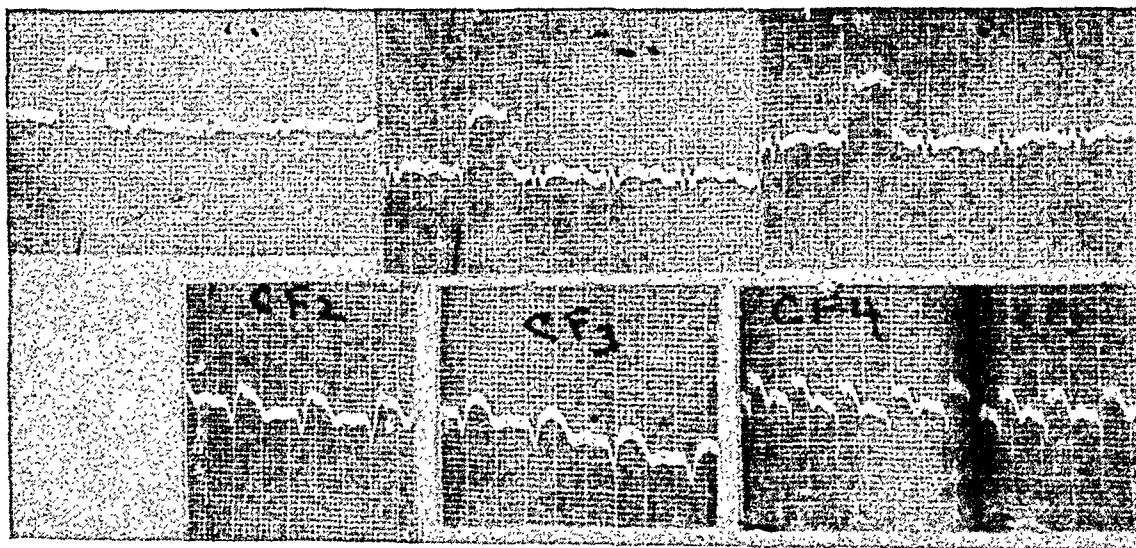


Fig. 1.—Electrocardiogram of April 4, 1945, showing an acute anterior wall infarction.

The brain was normal grossly. It was symmetrical. The arteries of the circle of Willis were the seat of moderate arteriosclerosis but no closure was found. Multiple sections were made at frequent intervals through all parts of the brain. No grossly visible abnormalities were found in the cerebrum, midbrain, pons, medulla, cerebellum, or upper cervical cord.

The other organs were not abnormal grossly.

Microscopic.—

Heart: One section was taken through the anterior wall of the left ventricle, passing through the occluded coronary artery (Fig. 2). The lumen of the artery contained laminated fibrin peripherally and fresh blood centrally. The endothelial cells were absent. The remainder of the intima was disorganized, vascularized, and infiltrated with small round cells and a few polymorphonuclears. The media was similarly disorganized, thinned, and infiltrated with inflammatory cells. The elastic tissue was fragmented and destroyed at many points. The adventitia was heavily infiltrated and thickened. At some points the cellular exudate consisted exclusively

of polymorphonuclears and was associated with necrotic cells and pyknotic nuclei. Gram stain revealed rare gram-negative rodlike structures which were not unequivocally bacteria. This inflammatory reaction extended into the surrounding epicardial fat. Elsewhere in the epicardium were scattered small round cells. The underlying myocardium at this point contained an interstitial exudate, chiefly of polymorphonuclear cells. The myocardial fibers, however, were only slightly degenerated and in the region of the most marked interstitial inflammation were essentially normal. A medium sized artery in the section showed fibrinoid necrosis of parts of the media without any inflammatory reaction. Another section was taken through the myocardium of the left ventricle laterally. The picture here showed extensive myocardial damage, ranging from acute swelling, edema, and necrosis of muscle fibers to a small round cell and polymorphonuclear infiltration of necrotic muscle and, finally, to vascular granulation tissue replacing the muscle. No large vessels were included in this section.

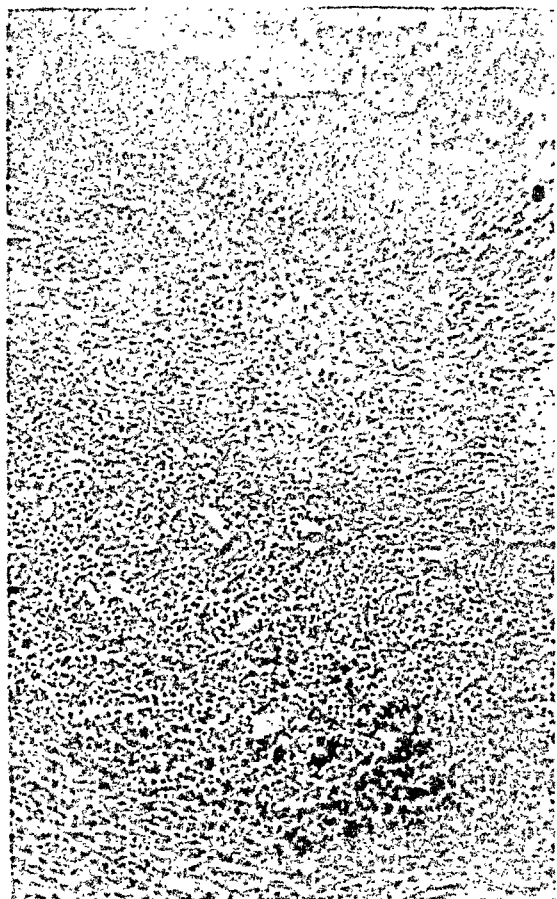


Fig. 2.



Fig. 3.

Fig. 2.—Section of left anterior descending coronary artery. The edge of the thrombus is above. Note the extensive polymorphonuclear exudate in the outer portion of the media and adventitia. Hematoxylin and eosin stain: $\times 400$.

Fig. 3.—Section of the kidney. In the center is a glomerulus which is disorganized, and collected both in and around it are polymorphonuclear cells. Hematoxylin and eosin: $\times 400$.

Liver: The general architecture was well preserved. There was a slight central atrophy of the lobules. There was marked fatty infiltration and degeneration of the liver cells which was focal and not limited to any part of the lobule. Rare arteriolar lesions consisting of thickening of the walls by polymorphonuclear leucocytes were found.

Spleen: The corpuscles were well preserved. The pulp was moderately congested. There was a considerable proliferation of plasma cells and histiocytes in the cords of Billroth. The arteries were thick-walled, with considerable proliferation and swelling of the endothelial cells. The section passed through the abscess noted grossly. The abscess was lined by fibrin and granulation tissue. Between this and the normal parenchyma was a thick zone of organizing hemorrhage. There were some areas of necrosis but little inflammatory response.

Kidneys: (Fig. 3.) The general architecture was intact. There were striking focal inflammatory lesions whose unit was the glomerulus and the surrounding tissue. These lesions consisted of marked round cell infiltration, at first near the hilus of the glomerulus, and later spreading around the glomerulus on all sides. In the glomerulus changes ranged from closure of the proximal capillary loops to necrosis of the entire structure. It was difficult to distinguish the afferent arteriole in these areas but it was apparently swollen and even occluded. Occasionally, a larger renal artery was involved, with destruction of the wall and marked granulomatous reaction. Except for these changes described the renal vessels were not unusual.

Gastrointestinal Tract: A section was taken through the hemorrhagic zone in the cecum. There was a superficial necrosis of the mucosa. The veins were markedly distended with blood. No inflammatory changes were found.

Bacteriology: From the splenic abscess there was isolated the same organism which had been present in the blood stream during life, *Salmonella choleraesuis*, variety Kunzendorf.

Diagnoses: 1. Septicemia, due to *Salmonella choleraesuis*, variety Kunzendorf.

- (a) Coronary arteritis, with thrombosis
- (b) Myocardial infarction, recent
- (c) Acute myocarditis
- (d) Focal embolic glomerulonephritis
- (e) Cloudy swelling and fatty degeneration of the liver
- (f) Splenic abscess

2. Cerebral arteriosclerosis.

COMMENT

An outline of the clinical course in this case has been presented. The upper respiratory infection and right otitis media started three weeks before admission, and ended one week after admission at a time when the fever and chills of the *Salmonella* infection were at their peak. It is apparent, in retrospect, that the first illness was not part of the second. The second illness began with fever, chills, and joint pains within a few days of admission. The temperature chart (noting the antipyretic effects of large doses of salicylates exhibited from March 27 to April 1) is obviously that of continuous fever. In view of the isolation of the *S. choleraesuis* organism whenever sought for in the blood stream from April 3 to April 24, it seems certain that this entire latter illness was a *Salmonella* infection.

The role played by sulfonamides is, of course, debatable. The patient certainly never received enough of the drug for adequate therapeutic effect against the *Salmonella* infection. The dose of 12 Gm. administered in the period before admission is very little to account for a febrile reaction. Furthermore, the normal formed elements of the blood, normal urine, and absence of skin eruption are evidence against any clinical role having been played by these drugs. Though the pathologic lesions somewhat resemble those ascribed by

Rich²⁻⁴ to sulfonamide reactions, they differ in the marked polymorphonuclear reactions and the picture of purulent thromboarteritis seen in our case. Also, there is the lack of focal liver necroses which we have come to associate so commonly with sulfonamide toxicity. The splenic abscess and positive cultures at autopsy, on the other hand, strongly favor a diagnosis of *Salmonella* etiology.

Periarteritis nodosa was also considered. Evidence against this diagnosis is the absence of eosinophilia in the blood or tissues, the finding of a causative organism, and the distribution and type of the lesions. The slides of the coronary artery, kidneys, and liver in our case were reviewed by Dr. Paul Klemperer, who feels that this is a true arteritis. Dr. Klemperer has seen other instances of infectious vasculitis due to *Salmonella* organisms.

SUMMARY AND CONCLUSIONS

A case of *Salmonella choleraesuis* septicemia is presented in which death was due to thromboarteritis of a coronary artery. The renal vessels were extensively involved in a similar process, and the hepatic vessels to a lesser degree. This particular type of specific lesion has not, to our knowledge, been previously described.

REFERENCES

1. Bornstein, S.: State of *Salmonella* Problem, *J. Immunol.* 46:439, 1943.
2. Rich, Arnold R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by 7 Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* 71:123, 1942.
3. Rich, Arnold R.: Additional Evidence of Role of Hypersensitivity in Etiology of Periarteritis Nodosa, Another Case Associated With Sulfonamide Reaction, *Bull. Johns Hopkins Hosp.* 71:375, 1942.
4. Rich, Arnold R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.* 72:65, 1943.

MASSIVE HYDROPERICARDIUM WITH COMPRESSION AND ANGULATION OF THE INFERIOR VENA CAVA

HARRY GREISMAN, M.D., CHESTER R. BROWN, M.D., AND
HANS SMETANA, M.D.
NEW YORK, N. Y.

THE effect of varying degrees of hydropericardium on the large venous trunks entering the right auricle of the heart is very accurately illustrated by the following case.

CASE REPORT

A 26-year-old Negro woman was admitted to the Lincoln Hospital on Jan. 1, 1940, because of swelling of the abdomen and dyspnea on exertion. The family history was irrelevant. The past history included the fact that the patient had been a heavy drinker. At the age of 3 years she had been observed in an institution because of a "swelling in the neck." She gave an indefinite history of syphilis. There was no history of a rheumatic infection. The present illness began a year and a half before admission, at which time the patient was hospitalized for seven weeks at another institution because of dyspnea and swelling of the abdomen and lower extremities. Physical examination at that time revealed a hydropericardium and enlargement of the liver. On x-ray examination the lung fields were clear. An electrocardiogram showed auricular fibrillation, ventricular extrasystoles, and low voltage. Several pericardial taps were done and the patient was discharged in an improved condition. The clinical diagnoses were: acute rheumatic heart disease, auricular fibrillation, and pericardial effusion.

On admission to Lincoln Hospital, the temperature was 101° F.; the pulse rate, 100; and the respiratory rate, 24 per minute. The pulse was completely irregular. The blood pressure was 105/60. There was marked edema of the abdominal wall and of the lower extremities. The neck veins were distended and there was slight exophthalmos. The heart was markedly enlarged and the lungs were congested. A short systolic murmur was audible over the precordium. The abdomen was enormously distended by fluid. The liver reached to the umbilicus.

Examination of the blood showed hemoglobin of 90 per cent, 5,000,000 erythrocytes, 7,000 white blood cells, and a normal differential count. Blood Wassermann and Kahn reactions were negative. Urinalysis showed a specific gravity of 1.010, a two-plus albuminuria, and no sugar. Bromsulfalein test revealed that 100 per cent of the dye was present in the blood in five minutes and 75 per cent in thirty minutes. Total proteins were 9.37 Gm. per 100 c.c.; urea nitrogen, 11 to 16 mg.; blood sugar, 81 mg.; cholesterol, 150 mg.; and icteric index, 12.5. A Mantoux test was positive at a dilution of 1:10,000.

Two determinations of the circulation time with 0.5 c.c. of paraldehyde were made. The drug was detected within 50 and 35 seconds, respectively.¹ Two determinations of the cubital venous pressure showed pressures of 31.5 cm. and 29.5 cm. of water, respectively. The electrocardiogram revealed auricular fibrillation, ventricular premature beats from multiple foci, extremely low QRS voltage, and flattened T deflections. An x-ray film of the thorax revealed the pericardium to be distended with fluid and so sharply delineated as to simulate marked elevation

From the Medical Service of Lincoln Hospital, Department of Hospitals, and the Department of Pathology, College of Physicians and Surgeons, Columbia University.
Received for publication Nov. 8, 1946.

of diaphragmatic domes (Fig. 1). An abdominal paracentesis was done on January 16, and 4 liters of clear amber-colored fluid were withdrawn; the fluid showed a 4-plus protein reaction and contained 170 leucocytes per cubic millimeter. The liver was then found to be markedly tender and to extend to the umbilicus. A second x-ray film on January 19 revealed no change in the thoracic outline. On February 13, 2,400 c.c. of greenish-yellow fluid was removed from the pericardial sac and half the volume replaced with air^{6,9} (Fig. 2). The patient was discharged April 14, 1940, somewhat improved.

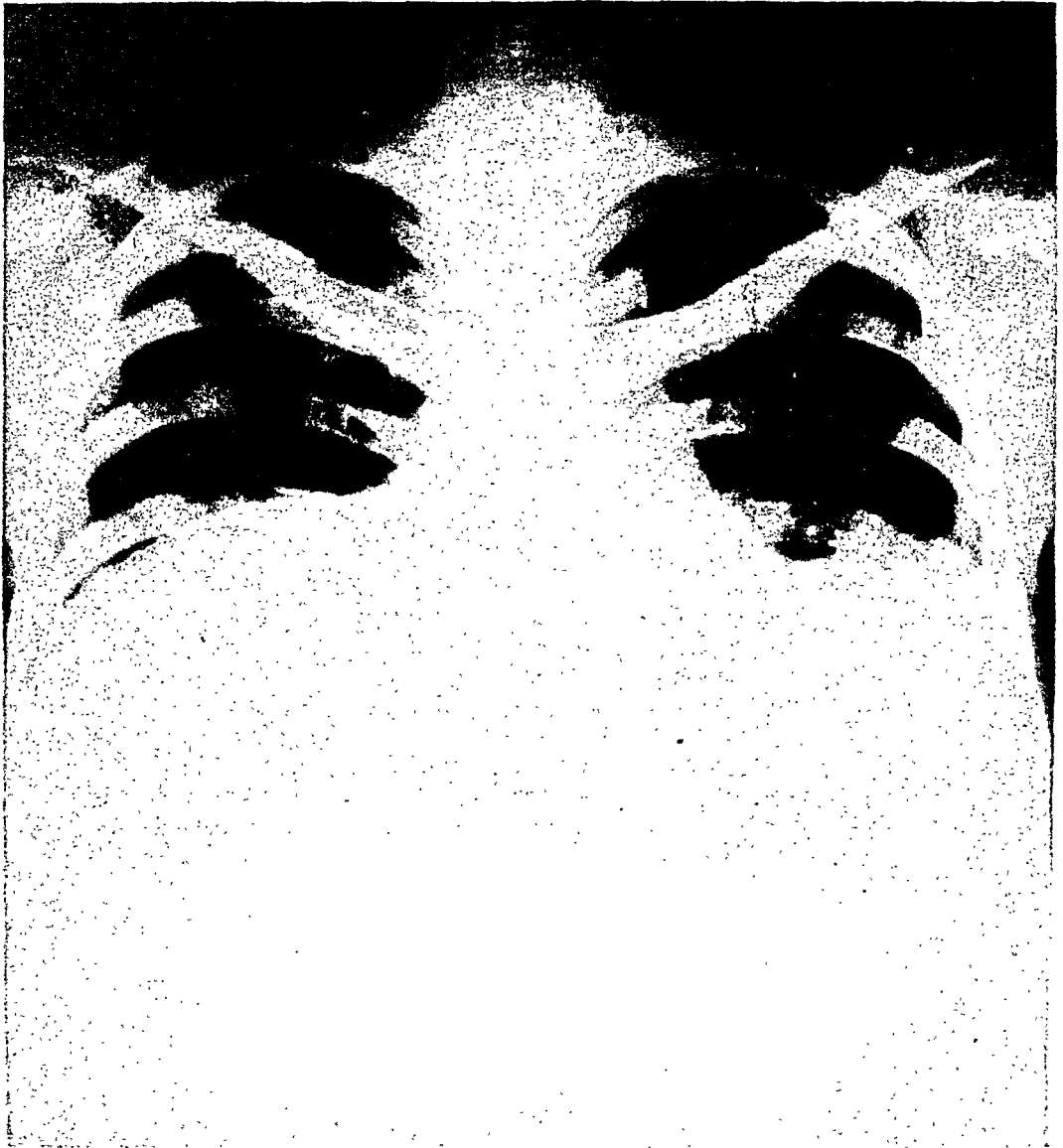


Fig. 1.—Jan. 9, 1940. Upright posteroanterior view of the chest. Extreme hydropericardium. Lateral borders of the pericardial sac are sharply demarcated.

After having remained at home for two months, the patient was admitted to the Presbyterian Hospital on Oct. 10, 1940. She was markedly cyanotic, dyspneic, and orthopneic, with an enormous abdomen on whose surface fine striae could be made out. Pitting edema extended up to the level of the scapular angles and involved the lower chest and abdominal wall. There was marked distention of the neck veins which did not pulsate and there was no edema of the upper

extremities. All accessory muscles were being used in respiration and the thorax seemed to move well. At both lung apices, breath sounds and moist râles were audible; at the lung bases, breath sounds were distant and there was diminution in resonance with absence of fremitus. No cardiac apex impulse or diastolic shock was felt. The borders of the heart were difficult to outline on percussion since the lower chest on both sides showed diminished resonance. However, there was an area of increased dullness which extended 7 cm. to the left and 6 cm. to the right of the midsternal line in the fifth intercostal space. Heart sounds were distant and of poor quality. The heart rate was extremely rapid and no murmurs were heard. The abdomen was hugely distended, tense, and nontender; a definite fluid wave was felt. No dilated veins were visible in the skin of the abdomen. After the removal of 14 liters of fluid by paracentesis, a firm, slightly tender, rounded liver edge could be made out about 7 cm. below the costal margin in the right midclavicular line. The spleen was not felt. There was no clubbing of the fingers. The tem-

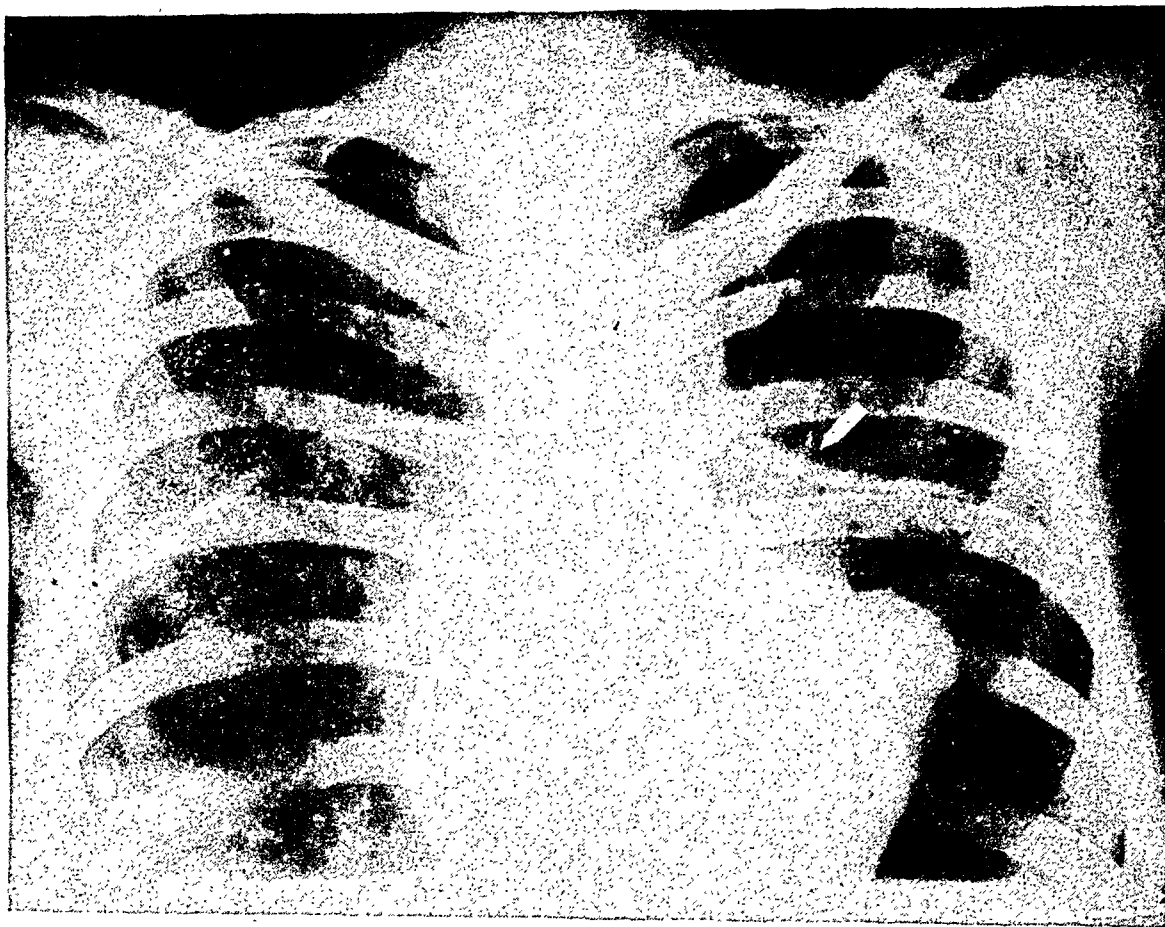


Fig. 2.—Feb. 13, 1940. Upright posteroanterior view of the chest. After removal of 2,400 c.c. of fluid from the pericardial sac and the injection of 1,760 c.c. of air, a hydropneumopericardium resulted. Note the thickened, greatly stretched parietal pericardium (arrow), and the large bulge to the right of the heart shadow (traction upon wall of right auricle).

perature was 98.8° F., the heart rate was 190 (the pulse could not be felt), and the respiratory rate was 44 per minute. The blood pressure was not obtainable. The sedimentation rate was 5 mm. in one hour. The Kline test was negative, blood nonprotein nitrogen was 42 mg. per 100 c.c., and blood sugar was 83 milligrams. A right thoracentesis yielded 600 c.c. of fluid which showed a specific gravity of 1.008 and 1,160 lymphocytes per cubic millimeter. The abdominal fluid showed a specific gravity of 1.015 and 440 lymphocytes per cubic millimeter. Guinea pigs injected with ascitic and pleural fluid remained well and showed no pathologic lesions at autopsy two months after injection.

The patient was so desperately ill that only a very brief physical examination was made. It was thought that the findings were consistent with a constrictive pericarditis with obstruction to the venous return, hydrothorax, and ascites.¹¹ After the conclusion of the paracentesis and thoracocentesis, the patient complained of marked fatigue, but said that her breathing was much improved and that she felt much stronger. She was placed in an oxygen tent and promptly fell asleep. A little more than two hours later, without much change in the clinical picture, she suddenly expired.

Autopsy.—The examination was performed six hours after death. On gross examination the abdomen was hugely distended and the skin showed many striae. The edema of the trunk, stopped rather abruptly at the level of the shoulder blades. In comparison to the markedly edematous lower extremities, the arms appeared disproportionately small. There was no clubbing of the fingers and toes, but the nailbeds were cyanotic.

The peritoneal cavity contained 750 c.c. of clear light fluid. The peritoneum was greatly thickened and its vascular pattern was quite prominent. The liver extended 14 cm. below the xiphoid and 9 cm. below the costal margin. The dome of the diaphragm was situated at the level of the sixth intercostal space on the right and the seventh intercostal space on the left side.

The thoracic cavity contained no free fluid in the pleural spaces. The lower portion of the thorax was taken up by a tremendously enlarged pericardial sac which was tightly filled with 3,000 c.c. of slightly cloudy, greenish-yellow fluid. The lungs were pushed up and their bases were at the level of the second intercostal space. On opening the pericardial sac, the heart was found to be pushed upward, and was represented by a round knob projecting into the pericardial space. The parietal pericardium was thickened and showed several large, yellowish plaques, varying in size from 1 to about 5 cm. in diameter, especially on the anterior, posterior, and diaphragmatic surfaces. Over these plaques the surface was irregularly granular. In several places the consistency of the membrane was cartilage-like, and masses of calcification were also felt. The remaining portion of the parietal pericardium was smooth and there were no adhesions between the epicardium and the pericardium. On inspection, in situ, a heavy fold of thickened pericardium covering the inferior vena cava could be seen to compress the lumen of this vein anteriorly and laterally at the level of the diaphragm; the same fold partly obstructed the lumina of the hepatic veins at the point where they emerge from the liver (Fig. 5). The weight of the heart and the attached pericardium was 600 grams. The heart was small and round, and its external markings were obliterated. The apex was rounded. The epicardium was greatly thickened, white in color, and opaque. Its surface was irregular, and contained many hyaline plaques and areas of calcification. The auricular appendages were small, rounded, and embedded in thickened epicardium. The thickening of the epicardium extended up to the trunks of the great vessels where it quite abruptly changed to a more normal membrane. The subepicardial fat tissue was normal in amount and was orange-yellow in color. The right auricle was pulled toward the right side by the inferior vena cava which could be seen and felt as a chord stretching across the right posterior pericardium. The cavity of the right auricle was greatly enlarged, but the wall was thin; its lumen was in broad communication with the inferior vena cava. The mouth of the superior vena cava appeared normal. The foramen ovale was closed and the coronary sinus was guarded by a curtain of Chiari. The auricular appendage was empty. The tricuspid valve was normal but the ostium was much too large for the valve, thereby producing a relative insufficiency. The right ventricle was small and appeared like an appendix to the auricle. It was otherwise normal. The pulmonary valve was delicate and competent and the pulmonary aorta was normal. The cavities of the left side of the heart were normal, as were the mitral and aortic valves. There were no signs of active or healed rheumatic endocarditis. The coronary arteries were normal. The myocardium was dark brown in color and there was no scarring. The lumen of the inferior vena cava at the level of its mouth measured 3.5 cm. in diameter. Sharp angulation of the vein at the point where it entered the pericardium severely compromised the lumen. Several white plaques were present in its intima just above the diaphragm. The superior vena cava was normal in caliber and appearance. The measurements of the cardiac ostia and walls were: tricuspid valve, 15.0 cm.; pulmonary valve, 5.5 cm.; mitral valve, 7.5 cm.; aortic valve, 5.5 cm.; left ventricle, 1.0 cm.; and right ventricle, 0.12 to .13 centimeter.

The lungs weighed 300 grams each. The pleura of the left lower lobe was moderately thickened and there was atelectasis of this lobe. Otherwise, both organs were normal. The bronchial and tracheal lymph nodes were small and not remarkable. There were no apical scars or any other signs of healed tuberculosis.

The spleen weighed 250 grams. Its capsule was thickened and a few irregular plaques resembling icing were present. On cross section the pulp was congested. The liver weighed 1,380 grams. Its capsule was irregularly thickened by whitish, opaque plaques; the surface of the capsule was irregularly granular. The liver tissue was firm in consistency. On cross section there was marked congestion and distention of the lobular portions. Opaque white tissue was seen in many of the lobules about the efferent vein, sometimes extending to the portal canals. The lumina of the hepatic veins were distended and their intima showed occasional yellowish-white plaques. A few well-circumscribed, yellowish-brown adenomas were present. The largest measured about 1 cm. in diameter. The gall bladder and bile passages were normal. No gross pathologic changes were seen in the pancreas, adrenals, or pelvic organs. The kidneys were congested. The mucosa of the gastrointestinal tract was markedly congested. The neck organs were normal. The brain and spinal cord were not examined. Postmortem aerobic and anaerobic cultures of the pericardial fluids showed no growth after eight days.

Microscopic Examination: In the left ventricle, the epicardium was greatly thickened by hyaline fibrous tissue in which there were areas of calcification. Areas of infiltration consisting of lymphocytes and plasma cells were present. On the borderline between epicardium and subepicardial fat tissue no tubercles were seen. The subepicardial fat tissue appeared normal and the branches of the coronary arteries seen in it showed no abnormalities. The heart muscle fibers were smaller than normal but their striations were distinct. The nuclei appeared normal and there was a moderate amount of lipochrome pigment about them. The right ventricle revealed vacuolization in the central portion of many of the myocardial fibers. The epicardium showed changes similar to those found in the left ventricle. The auricles exhibited vacular degeneration of the muscle fibers; at times the cross striations were not well seen. No Aschoff bodies were seen in any of the sections. Sections of the valves showed no significant pathologic changes. The pericardial sac was greatly thickened by hyaline fibrous tissue and infiltrations consisting of lymphocytes and plasma cells were present in it. The diaphragm showed occasional degeneration of muscle fibers. There were no tubercles. The inferior vena cava, in a section taken from the mouth of the vein, showed thickening of the intima by plaques which were composed of smooth muscle fibers and hyaline fibrous tissue. These plaques extended partly into the media. The aorta was normal. The lungs showed moderate congestion of the capillaries and occasional lymphocytic infiltrations about blood vessels and bronchi. There was sclerosis of some of the pulmonary venules. The spleen showed marked congestion. The liver was greatly congested and showed cardiac cirrhosis. Many of the portal canals seemed larger than normal and were composed of rather dense fibrous tissue, in which there was occasional slight proliferation of bile ducts. In several places the sections presented the picture of definite portal cirrhosis. The pancreas, adrenals, kidneys, pelvic organs, and the gastrointestinal tract all showed varying degrees of congestion, but no other relevant changes. The bone marrow was active and showed the usual variety of hematopoietic cells.

Anatomic Diagnoses: Chronic pericarditis with calcification, etiology unknown. Brown atrophy of the heart. Hydropericardium, with compression and angulation of the inferior vena cava. Pick's syndrome—clinical. Ascites, anasarca, and chronic passive congestion of liver, spleen, kidneys, and intestines. Cardiac cirrhosis, portal cirrhosis and adenomas of the liver. Keloids.

DISCUSSION

Massive pericardial effusions occur most frequently in rheumatic heart disease and tuberculosis of the pericardium. Smaller effusions occur less frequently in the terminal stage of congestive heart failure, pyogenic infection,

uremia, emphysema, and myxedema. Variation in amount and position of fluid within the pericardial sac may cause diverse subjective and objective signs of circulatory insufficiency. The mechanism of the circulatory disturbances attributable to variable amounts of fluid within the pericardial sac has been the subject of extensive clinical and experimental study.¹

There are two chief types of pericardial effusion: the central (Fig. 3,A) and peripheral (Figs. 3,B and 4). In the central type, usually caused by rapidly accumulating massive effusion, the heart is primarily compressed, particularly the right auricle. The resulting circulatory congestive failure is uniform and generalized. Both venae cavae are equally dilated and congested. In the peripheral type, a small amount of fluid may seriously compress both venae cavae and hepatic veins. Visceral congestion is localized and concentrated on the radicals of the compressed veins. The dome of the right diaphragm and the diaphragmatic surface of the liver may be compressed and flattened simultaneously, constricting the lumen of the left hepatic vein which, during its terminal course, runs almost parallel to the surface of the liver. This narrowing of the ostia of the hepatic veins leads to congestion of the liver, which then rapidly increases in size and becomes painful (Figs. 3,B and 4). Enlargement of the liver, which is usually greater than in cases of decompensated mitral stenosis, is then followed by ascites without significant cyanosis. Compression of the supradiaphragmatic portion of the inferior vena cava affects the return of blood from all its radicals, causing congestion and edema of the lower extremities, especially in the upright position. In addition, pressure of the increasing ascites on the abdominal portion of the inferior vena cava adds to the circulatory embarrassment. The edema of the lower extremities may rapidly recede when the patient is in the horizontal position, especially if the hydropericardium is not extreme, allowing the fluid within the pericardial sac to shift, thereby relieving the pressure on the pericardial funnel and on the inferior vena cava. However, there may be residual cyanosis due to the restricted space within the pericardial sac.² The shift of the pericardial effusion produces static changes affecting the superior vena cava. In the early stages of hydropericardium the patient may show nocturnal facial edema and cyanosis, with rapid recession during the day when in the sitting or upright position.

Extreme hydropericardium of the central type (Fig. 3,A) produces persistent compression of both the inferior and superior vena cava, followed by congestion of the jugular veins and severe cyanosis with cephalad edema. Flow of blood to the lungs is thus reduced and pulmonary congestion is not observed in hydropericardium unless left ventricular failure occurs. If the left heart functions well, and if the pulmonary veins are somewhat compressed by the pericardial fluid, the lungs may appear even paler than normal. Primary right ventricular insufficiency with auricular and caval dilatation may produce similar consequences which, however, do not occur as rapidly nor to as marked an extent as those produced by the peripheral type of stasis.

In the present case, in addition to the effect of the pressure of the massive hydropericardium on the inferior vena cava and the hepatic veins, there was a

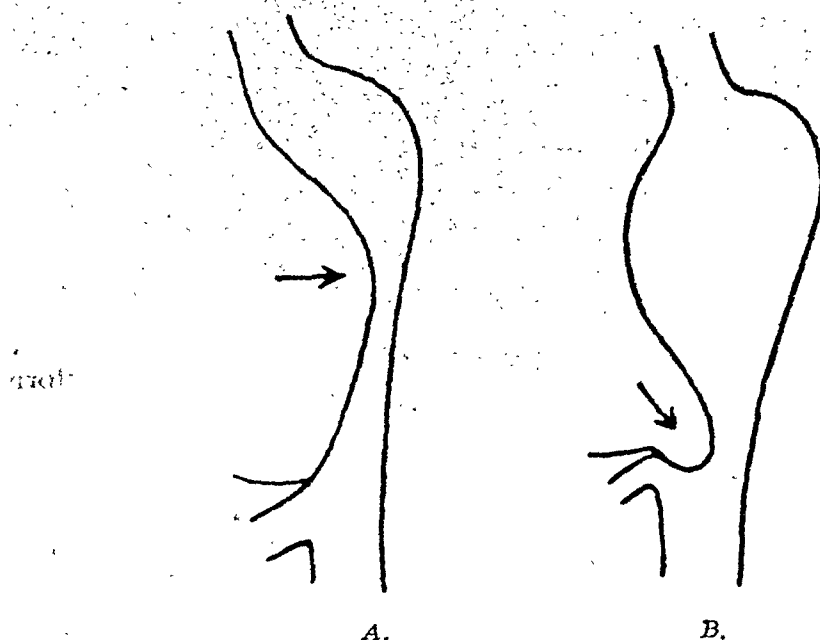


Fig. 3.—Schematic drawing (Elias and Feller) of the, *A*, central and, *B*, peripheral types of cardiac stasis caused by hydropericardium. Arrows indicate pressure points upon right auricle, inferior vena cava, and hepatic vein. The superior vena cava (above) and inferior vena cava (below). Heart tamponade, *B*, is caused by pressure of a large amount of fluid on the auricle. A smaller amount of fluid, *A*, drives a wedge into and compresses the inferior vena cava as well as the ostia of the hepatic veins, one of which is portrayed opening subdiaphragmatically into the vena cava. Note constriction of the inferior vena cava above the diaphragm and its dilatation below. Usually the left hepatic veins are more compressed than the right.

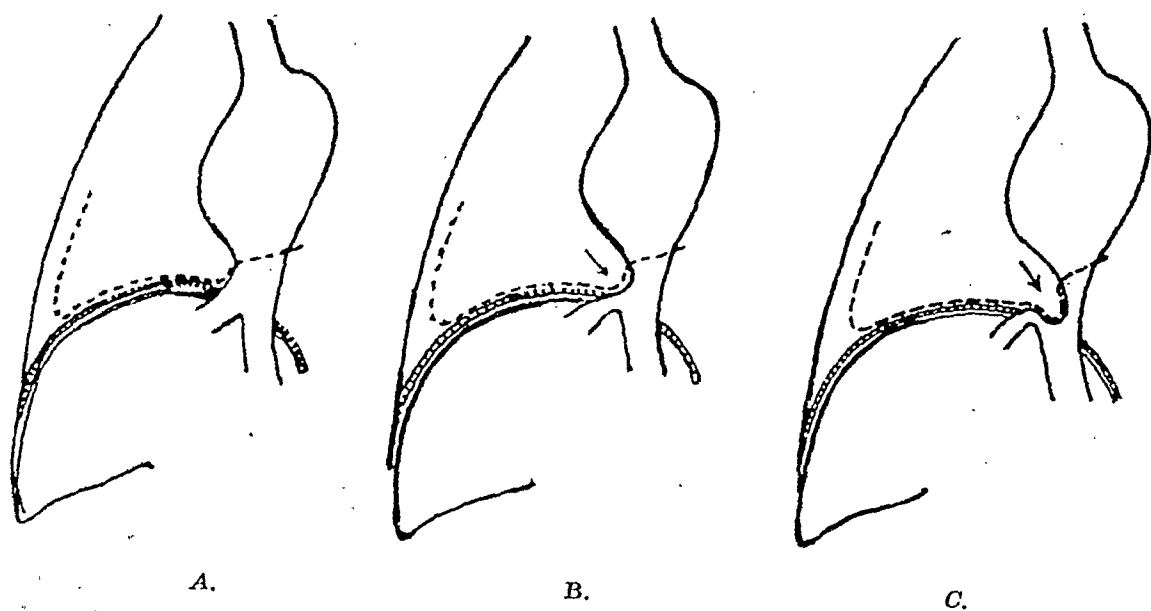


Fig. 4.—Schematic drawing (Elias and Feller) illustrating pressure effects within pericardial sac in the peripheral type of congestion. *A*, Normal relations. Superior (above) and inferior vena cava (below). The latter receives a tributary of the hepatic vein (left). *B*, Moderate effusion in exudative pericarditis. *C*, Massive effusion within the sac (experimental). At onset, a small amount of fluid collects at the base of the sac without appreciable effect. Larger amounts accumulate within the right and the dorsocaudal portion of the sac and exert pressure on the ostia of the hepatic veins prior to involvement of the inferior vena cava. Congestion of the liver precedes edema of the legs. Arrows indicate pressure points. Note angulation (pressure) of the inferior vena cava.

severe kinking of the inferior vena cava (Fig. 5) produced by a considerable traction upon the wall of the right auricle. The marked dyspnea and orthopnea, which were so extreme in this case, were related to the insufficiency of the tricuspid valve in addition to the tamponade effect of the fluid. The compression of the inferior vena cava, together with the narrowing of orifices of the hepatic veins, readily accounts for the extreme passive congestion and edema of the lower extremities, the trunk, the liver, and the ascites.

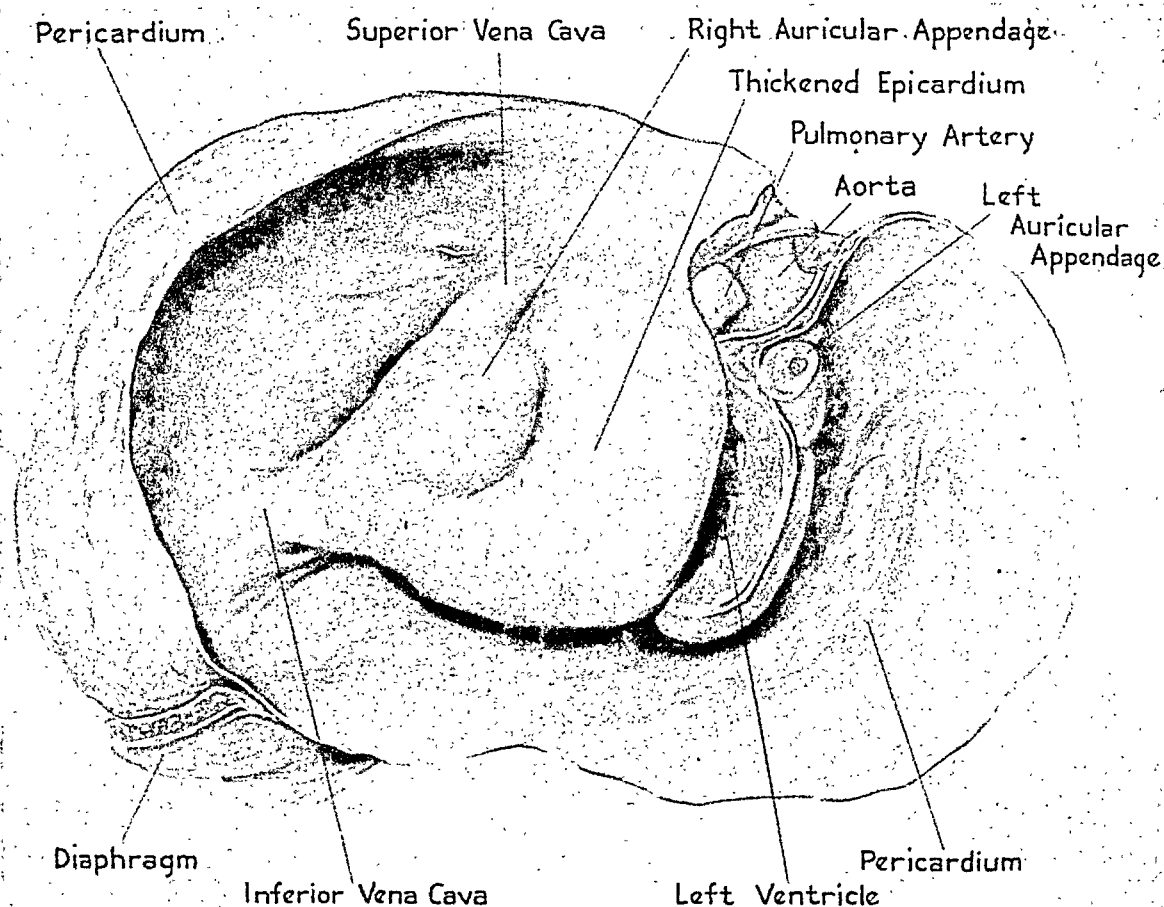


Fig. 5.—Extreme hydropericardium with angulation and compression of the inferior vena cava.

The pericardial disease in this case was obviously of a chronic nature, as evidenced by the extreme distention of the sac and marked fibrous thickening of its wall as well as by the areas of hyalinization and calcification.⁶ The etiology of the pericardial disease is obscure. It is unlikely that rheumatism was the causal agent because of the absence of rheumatic changes of the valves and myocardium. Despite the history of syphilitic infection a syphilitic etiology is unlikely; the serologic reactions for syphilis were negative and no other syphilitic manifestations were found. No gross or histologic evidence of active or obsolete tuberculosis was discovered at autopsy.¹⁰

SUMMARY

1. A case of massive hydropericardium of obscure etiology and long duration is described.

2. Hydropneumopericardium was induced and characteristic roentgenograms were obtained.

3. The physiologic mechanisms involved are reviewed with particular emphasis on the central and peripheral types of hydropericardium. Isolated and disproportional visceral congestion and edema is explained by the latter type and differentiated from the usual congestive mechanism in decompensated heart failure. The traction upon the wall of the right auricle found at autopsy was an additional mechanical factor heretofore not emphasized.

REFERENCES

1. Elias, Herbert, and Feller, Adolf: *Stauungstypen bei Kreislaufstörungen*, Berlin, 1926, Julius Springer.
2. Conner, L. A.: On the Diagnosis of Pericardial Effusion, *AM. HEART J.* 1:421, 1926.
3. Fenichel, N. M., and Epstein, B. S.: The Clinical and Roentgenologic Diagnosis of Pericardial Effusion, *Ann. Int. Med.* 24:401, 1946.
4. Stewart, H. J., Crane, N. F., and Deitrich, J. F.: Studies of the Circulation in Pericardial Effusion, *AM. HEART J.* 16:189, 1938.
Zucclòla, P. F.: Treatment of Pericarditis With Effusion by Means of Pneumopericardium, *Riforma med.* 41:607, 1925.
6. Fineberg, M. H.: Functional Capacity of the Normal Pericardium: An Experimental Study, *AM. HEART J.* 11:746, 1936.
7. Smith, Harry L., and Willius, F. A.: Pericarditis; Pericarditis With Effusion, *Arch. Int. Med.* 50:192, 1932.
8. Wenckebach, K. F.: Beobachtungen bei exsudativer und adhasiver Perikarditis, *Ztschr. f. klin. Med.* 71:402, 1910.
9. Troisier, J., Jacquelin, A., and Gayet, R.: Pericardite serofibrineuse. Pneumopericarde artificiel. Symphyse consecutive. L'hémiplégie pericarditique, *Bull. et mém. Soc. méd. d. hôp. de Par.* 47:263, 1923.
10. McDonald, R. H.: Pericardial Effusion of Unknown Etiology Necessitating Repeated Paracentesis, *AM. HEART J.* 6:561, 1931.
11. Rohde, Carl: Die Stauung der unteren Hohlvene vor dem rechten Herzen und ihre Bedeutung im Krankheitsbilde der Pericarditis adhaesiva, *Deutsche Ztschr. f. Chir.* 203-204:18, 1927.

Abstracts and Reviews

Selected Abstracts

Ratliff, R. K., Nesbit, R. M., Plumb, R. T., and Bohne, W.: Nephrectomy for Hypertension With Unilateral Renal Disease. *J. A. M. A.* 133:296 (Feb. 1), 1947.

Of 2,055 pyelographic studies carried out in a five-year period, only 9 per cent of all the patients studied had abnormalities, while less than five per cent were candidates for nephrectomy and fewer came to operation.

Nephrectomy was performed on eleven patients who had hydronephrosis with significant hypertension. Five patients showed no permanent lowering of the blood pressure following operation, while two patients had moderate improvement and four had normal blood pressures which have persisted since the operation.

Of the latter group, two are significant in that they were known to have had normal levels of blood pressure prior to the development of advanced hydronephrosis and were followed for a time during which the development of hypertension paralleled the development of advancing hydronephrosis. In each of these instances, nephrectomy was followed by a return of the blood pressure to normal.

These authors suggest that routine urologic studies be performed on all hypertensive patients since a significant number of the patients having gross renal lesions could not otherwise be discovered.

BELLETT.

Collins, C. G., Nelson, E. W., Jones, J. R., Weinstein, B. B., and Thomas, E. P.: Ligation of the Vena Cava—A Critical Evaluation Based on a Study of 22 Cases. *New Orleans M. & S. J.* 99:488 (April), 1947.

The authors feel that patients with post-partum or postabortal sepsis who fail to respond to nonsurgical measures should be considered as candidates for ligation of the normal venous return from the uterus, the vena cava, and both ovarian veins. In addition to suppurative pelvic thrombophlebitis, these authors believe that ligation of the vena cava is indicated in cases of phlebotrombosis if the clotting process has extended into the external iliac or common iliac veins.

Of the twenty-two cases discussed, ligation was performed only in cases which failed to respond to all nonoperative measures advocated for suppurative pelvic thrombophlebitis, and these patients were the most acutely ill of all cases of puerperal sepsis seen by these authors. In the two patients in whom ligation was done for phlebotrombosis of the common femoral vein associated with uterine fibroids and the one case of postoperative suppurative pelvic thrombophlebitis, there were no deaths. In the nineteen patients with puerperal suppurative pelvic thrombophlebitis who were operated on, there were four operative deaths. All patients showed remarkably good compensation of the circulation following ligation. The end results and the appearance of the patients' extremities were very good.

The authors state that ligation of the inferior vena cava carries a low operative mortality and this procedure is one that should be used without hesitation when indicated. The minimal amount of edema and circulatory disturbance occasioned by vena cava ligation, they believe, was due to the fact that at the time of operation the sympathetic chains were sectioned. If this is not possible at operation, they suggest routine blocking of the lumbar sympathetics bilaterally daily for five or six days after operation.

BELLETT.

Johnson, A. L., Wollin, D. G., and Ross, J. B.: **Heart Catheterization in the Investigation of Congenital Heart Disease.** *Canad. M.A.J.* 56:249 (March), 1947.

This report is based upon a group of seventeen children with congenital heart disease, in which this method of study has been employed. The patients ranged in age from 19 months to 16 years. Four were cyanotic and the remainder acyanotic. During the investigation all four heart chambers were entered, as well as the pulmonary artery and its branches, and the pulmonary veins.

In the study of a congenital heart by this means, samples of blood were withdrawn from various parts of the heart and pulmonary tree. From a correlation of the oxygen content of the blood with the pressure exerted and the site of the catheter at the point where these observations were made, the course of the blood flow might be traced.

The procedure employed is similar to that described by Cournand and Ranges. The median cubital vein of either arm or the saphenous vein in the thigh is exposed, and a uretal type of catheter is introduced through a nick in the vein. The catheter is introduced *under fluoroscopic vision*, passing into the right auricle, right ventricle, and the pulmonary artery and its branches.

Penicillin is given intramuscularly for forty-eight hours following the procedure, 5,000 to 10,000 units every three hours, depending on the age of the child. The pressure is recorded by a saline manometer and a Tycos dial.

Right heart catheterization is generally regarded as a safe procedure.

These authors report no arrhythmias, apart from extrasystoles due to the stimulation of heart catheterization. In one case a paroxysmal tachycardia occurred after the catheter had been placed in the right auricle and apparently through the auricular septum into the left auricle.

Furthermore, apart from occasional instances of slight thrombophlebitis of the brachial vein, no residua of trauma to endothelial linings have been described. In this respect the authors report a case of an ill, markedly cyanotic infant weighting 19 pounds, with a hemoglobin of 22 Gm. per cent. The catheter was introduced into the right saphenous vein near the femoral junction and passed into the right auricle. The infant was heparinized for the duration of the procedure. One month following this procedure death occurred. Autopsy revealed a clinically unsuspected, well-organized thrombus occluding the inferior vena cava, both common iliac veins, and the right renal vein, and a large thrombus attached to the right auricular wall at the base of one leaflet of the tricuspid valve.

Of the seventeen patients studied, nine were considered to have interventricular septal defects, in one there was evidence of an associated interauricular septal defect, and in another, the presence of a persistent left superior vena cava was demonstrated.

The evidence for the presence of a ventricular septal defect is arterialized blood in the right ventricle, or blood with a significantly higher oxygen content than that found in the right auricle.

In the course of this study, the authors observed during the placing of the catheter under fluoroscopic vision, that an excellent estimate of the size of the right ventricle could be made.

This method of heart catheterization, in the experience of the authors, appears a most useful adjunct in the investigation of congenital heart disease.

BELLET.

Dungal, Niels: **Cardioaortitis.** *Arch. Path.* 42:495 (Nov.), 1946.

The author reports a case of marked productive inflammation, particularly of the abdominal aorta. A man, 22 years of age, had had recurring attacks of polyarthritis with fever for ten years. In addition, glandular enlargements, particularly in the neck, made their appearance and became more or less chronic. Following recurring arthritis there was moderate secondary anemia and leucopenia, the cause of which remained uncertain. All bacteriologic and serologic diagnostic testing was negative. The patient eventually died of uremia.

Autopsy revealed cardiac hypertrophy, large nephrotic kidneys infiltrated with amyloid, an enlarged spleen weighing 700 grams, and caseous lymph nodes in the neck and in the mediastinum. Of particular interest was a productive inflammatory thickening of the walls of the abdominal aorta. Repeated section of the aortic wall did not reveal evidence of the ordinary atherosclerotic and calcific changes usually encountered in degenerative aortic disease. Microscopically the lesion was featured by increased thickness of the wall due mainly to thickening of the intima.

The thickening was mainly the result of hyaline infiltration containing foci of cellular infiltrations; consisting of neutrophil leukocytes, endothelioid cells, and histiocytes in a background of necrotic tissue, accompanied by hemorrhages of varying degree. The vasa vasorum were frequently surrounded by plasma cells and small heaps of lymphocytes. The muscular tissue was largely replaced by fibrosis and numerous small and large fluid-filled spaces were seen, suggesting colliquative necrosis. Microscopic examination of the myocardium revealed numerous small interstitial accumulations of lymphocytes and monocytes and a few plasma cells.

The writer points out that syphilis, which is considered the most common cause of productive aortic inflammation, was clearly absent in this case and that clinically no evidence of syphilitic infection had been found. It was felt with equal certainty that another great cause of microscopic aortitis, rheumatic fever, was absent in this case since there was no cardiac valvular pathology. Due consideration was given to the clinical history of recurring polyarthritis. The author did not feel justified in assuming that streptococcic infection might be the basis of the changes, since cultures from the spleen and the heart remained sterile.

Dungal selected similar cases from the literature in which various authors were convinced that syphilis played no role in the development of the aortic lesions. He believes this may be a case of focal aortitis related to the lesions of vascular allergy as described by Rich. The presence of chronic tuberculous infection, in the author's opinion, did not appear to have any causal relationship. He emphasized the growing caution in the minds of many pathologists against making a blanket diagnosis of syphilitic aortitis where the aorta shows an obvious, but not clearly defined, type of inflammation.

GOULEY.

Deschamps, P. N.: A Case of Prolonged Flutter. Arch. d. mal. du coeur. 39:233 (July-Aug.), 1946.

An unusual case of auricular flutter is reported in which the abnormal rhythm persisted for a period of over two years. The patient, a 36-year-old woman, had rheumatic heart disease with mitral stenosis and insufficiency. The auriculoventricular response was 2:1 during exercise and 4:1 at rest. It was noteworthy that, with the exception of occasional brief intervals of mild congestive failure, the patient was able to continue her daily activities with little or no discomfort. More remarkable was the fact that repeated attempts to terminate the arrhythmia by digitalis and quinidine therapy were totally ineffectual and that ultimately, at a time when no medication was being taken, the arrhythmia ceased spontaneously.

LAPLACE.

Macht, D. I.: Thromboplastic Properties of Digitaloids and Mercurial Diuretics Employed in Cardiology. Arch. internat. de pharmacodyn. et de therap. 72:297 (Sept.), 1946.

Experimental studies on cats and rabbits were undertaken to supplement the previous observations of the author on the thromboplastic properties of digitalis. It was found that digitalis and ouabain injection caused a progressive shortening of the coagulation time of whole blood which paralleled the repeated injections. The minimum lethal dose of digitalis and ouabain for a heparinized cat was larger than for a normal cat; this increased tolerance was attributed to inhibition of the thromboplastic effect. The mercurial diuretics, mercupurin, mercurhydrin, and salyrgan, likewise accelerated blood clotting. They decreased the prothrombin time, decreased antiprothrombin, and increased blood fibrinogen, but did not affect the platelet count or the blood calcium. Occasional instances of sudden death in the course of digitalis or mercurial diuretic therapy are attributed to this thromboplastic action.

LAPLACE.

MacMillan, R. L.: Adrenal Apoplexy Associated with Hypertension. Lancet 1:177 (Feb.), 1947.

The author presents the history of a 60-year-old patient with pre-existing hypertension who suddenly developed severe upper abdominal pain which later became localized in the epigastrium. A clinical diagnosis of coronary occlusion was made. On the following day, after developing shock, the patient died. Autopsy revealed hemorrhage in both adrenal glands as the cause of death. This case is considered to be of interest since it emphasizes the fact that adrenal hemorrhage may occur in other conditions than septicemia (Friderichsen-Waterhouse syndrome).

The author states that adrenal apoplexy has never been diagnosed either clinically or at operation. He suggests that adrenal hemorrhage may be (1) associated with involution or destruction of gland substance in (a) the newborn, (b) pregnancy, (c) invasion by tumor; (2) caused by damage to blood-vessel walls by (a) toxemia (burns), (b) trauma, (c) septicemia (Friderichsen-Waterhouse syndrome), (d) arteriosclerotic change; (3) associated with hypertension; (4) associated with a generalized hemorrhagic tendency, as in leukemia and in vitamin K deficiency in the newborn.

BELLET.

Gurvich, N. L., and Yuniev, G. S.: Restoration of Heart Rhythm During Fibrillation by a Condenser Discharge. Am. Rev. Soviet Med. 4:253 (Feb.), 1947.

In 1938 these authors developed a condenser method for terminating cardiac fibrillation caused by electric shock. They used a condenser battery with a capacity of 3-4 microfarads. The condensers were charged by a small step-up transformer, with the aid of a rectifier. In order to restore the heart function the condenser had to be charged with more than 2,000 volts, depending upon the size of the animal. Later, these authors studied in detail the physical and physiologic conditions which terminated cardiac fibrillation by a condenser discharge.

Six hundred fifty dogs, sheep, and goats were used. In the majority of cases no narcotics were given. Cardiac fibrillation was produced by passing through the electrode an alternating current of 0.1 amperes or greater intensity. Fibrillation was stopped by condenser discharges. Capacity fluctuated between 0.5 and 52 microfarads; the tension which was applied reached as high as 6,000 volts.

The importance of the prolongation of discharge for the termination of fibrillation was indicated. The condenser discharge restored cardiac function if the discharge was applied not later than one to one and one-half minutes after the onset of fibrillation. However, by means of preliminary massage of the heart, normal cardiac function may be restored by discharges applied after a considerably longer period of fibrillation.

The above tests made on fifty dogs showed that after fibrillation lasting 8 minutes, the animals were easily resuscitated. When it had lasted ten to fifteen minutes nineteen animals survived and seventeen died. Thirteen of the latter had been weakened by previous operations.

The condenser discharge is effective in checking cardiac fibrillation in animals caused by electric shock as well as by certain poisons (chloroform, potassium chloride). The cardiac rhythm returned and resembled the original rhythm which was recorded before the occurrence of fibrillation. The re-establishment of normal heart action and of the function of the central and sympathetic nervous systems is lasting, as indicated by animals observed from ten days to four months.

The experiments suggest that the condenser method of reestablishing the normal heart action in ventricular fibrillation may be just as effective in cases of electric shock in man.

BELLET.

Teplich, J. G., and Drake, E. H.: The Roentgen and Cardiac Manifestations of Funnel Chest. Am. J. Roentgenol. 56:271 (Dec.), 1946.

The authors present a review of nine cases of funnel chest. The roentgen changes, electrocardiographic and clinical findings, and the salient features of the literature are presented.

This deformity greatly lessens the anteroposterior diameter of the chest and displaces the heart to the left. Rotation of the heart along its long axis may also result.

The x-ray findings are quite characteristic. In the posteroanterior view the heart is shifted to the left with elevation of the left border. Unless the true situation is realized, this configuration may erroneously be interpreted as congenital heart disease, mitral disease, or an enlarged heart.

Minor electrocardiographic abnormalities are frequently present, particularly in the chest leads. These are due to a shift of the heart to the left and rotation on the long axis, rather than to myocardial pathology. The authors describe an unusual case with bigeminal rhythm due to

regularly recurring right ventricular extrasystoles, which was probably due to an irritable focus in the right ventricle resulting from constant pressure of the deformed sternum in this region.

The authors feel that uncomplicated nontraumatic developmental funnel chests usually do not produce symptoms of a serious nature and surgical elevation of the sternum is rarely indicated.

ZION.

Puddu, V., Mussafia, A., and Giordano, G.: An Unusual Electrocardiographic Pattern of Myocardial Infarction. (Type QT₁C₃₋₆). Cardiolgia 11: 133, 1947.

Three patients are reported with definite electrocardiographic changes of an anterior wall infarct in the limb leads and with normal chest leads (CF₃ and IVF, or CR₃ and IVR). It is pointed out that these changes combine some of the features of an anterior wall and supra-apical infarction pattern (normal IVR). The changes in the limb leads point to a localization not far from the apex and might be near the apex in the lowest portion of the lateral wall. The terms "lateral para-apical" or "inferior lateral" infarction are suggested. This view is further supported by a series of normal and pathologic patients in whom Lead CF₃ was taken. They usually showed identity of form of QRS in Leads I and CF₃. Two further patients are reported with anterior wall infarction pattern in the limb leads, normal CR₃ and IVR, and Leads CR₃ or CR₆ resembling Lead I.

Only five such cases were found in more than 200 cases of infarction and, therefore, are considered rare.

LENEL.

Sanabria, A.: 2-Thiouracil in Heart Failure and in Angina Pectoris. Cardiolgia 11:143, 1947.

Seven patients with heart failure or angina pectoris treated with thiouracil are reported. Whenever a fall of the basal metabolic rate (in one case as low as —28 per cent) was obtained, definite improvement of heart failure and angina pectoris followed. The basal metabolic rate fell several weeks after administration of thiouracil was started. This was associated with an increase in blood cholesterol.

Two patients showed evidence of drug toxicity and no reduction in the basal metabolic rate. In both the drug was discontinued. One patient died on the eighteenth day of therapy. Four patients had a satisfactory response.

In conjunction with thiouracil therapy, liver extract, folic acid, piridoxine, bone marrow extract, vitamin C, sodium bicarbonate, and a low fat diet are given.

LENEL.

Lindgren, I.: High Oxygen Concentration Under Normal and Increased Respiratory Pressure in Cardiac Pain and in Pulmonary Edema. Cardiolgia 11:127, 1947.

The pain in angina was relieved and the electrocardiogram with typical signs of coronary insufficiency at rest showed improvement during oxygen administration. The beneficial effect of 100 per cent oxygen administered under increased respiratory pressure was demonstrated in a case of coronary occlusion with pulmonary edema.

It is pointed out that 100 per cent oxygen increases the oxygen saturation in the blood and plays an important role under pathologic conditions. Increase in oxygen tension during positive pressure administration tends to increase the oxygen saturation of the arterial blood. A closed or semiclosed system must be used when positive pressure is given. It is pointed out that the vicious circle in pulmonary edema is interrupted by the use of oxygen under positive pressure. In the previously mentioned patient 10 mm. Hg positive pressure was used; this can be administered only in unconscious patients.

This therapy has also been found beneficial in eclampsia with or without cardiac failure. The case of a primipara is reported who had been unconscious for twenty-two hours after delivery with attacks of eclampsia and progressive pulmonary edema. Strophanthin, hypertonic glucose, venesection, and oxygen by nasal catheter had no effect. 100 per cent oxygen under 10 mm. Hg pressure produced rapid and striking improvement.

LENEL.

Batt, R. C.: A Roentgenkymographic Study of the Heart in Myasthenia Gravis. Radiology 46:374, 1947.

Early kymographic studies of myasthenic patients showed a slight slowing of the pulse with minor but definite changes in the wave form along the left ventricular border after a test dose of prostigmine. Similar kymographic changes could be obtained in normal subjects used as a control; thus indicating that the changes were due to the pharmacologic effects of prostigmine. There were, however, wave form changes which at first could not be accounted for. It is well known that any change in the ratio between the grid speed and the heart rate will affect the appearance of the kymographic wave form. Patients with myasthenia gravis, as well as normal patients, were studied before and after prostigmine test doses with various grid speeds. The results in all cases were identical. This indicated that the major changes in shape of the kymographic wave produced by prostigmine represents artefacts due to the changing ratio between heart rate and grid speed.

These studies showed that there are no characteristic findings in the cardiac roentgenkymograms of patients with myasthenia gravis. The prostigmine test produces no characteristic cardiac kymographic wave changes in either normal or myasthenia gravis patients. The test doses may slow the cardiac rate and thereby produce deceptive changes in wave form.

ZION.

Terroux, K. Godwin, Gertler, M. M., and Hoff, H. E.: The Alkali Tolerance of the Dog Heart. Am. J. Physiol. 148:1 (Jan.), 1947.

In determining the alkali tolerance of the dog heart in situ, twenty-four dogs were used by the authors, and these were infused with 0.3 normal sodium hydroxide in most cases. Blood samples were drawn from a femoral artery, as were the samples for lactate determinations. Electrocardiograms were taken from Lead II at intervals corresponding to 50 c.c. increments of infusion fluid.

The results of the experiments fall into three groups. In Group I the dogs died in the initial stages of the experiment, either because of a high initial rate of alkali infusion or because of some individual sensitivity to alkali. Severe anoxia occurred in all these cases. In Group II the infusion rates were low and blood lactate did not rise above 100 mg. per cent. These hearts failed at pH values between 7.7 and 7.93. In Group III the overall injection rates were higher than in Group II. These animals showed rigor of the respiratory muscles, as well as of some other muscle groups, accompanied by an increase in the blood lactate level with values up to 200 mg. per cent. The blood pH rose as high as 8.12 to 8.40 before heart failure. Blood pressure was well maintained until the final failure of the heart. In the electrocardiogram, the most interesting changes were in the T wave which became lower in amplitude as the pH rose, with complete reversal of polarity either before or at the time of the first maximum pH. RS-T segment depressions were observed just before heart failure occurred, indicating that this was significant of impending trouble. The R wave changed only in the final stages. Heart rate was essentially unchanged. Intraventricular conduction time was unchanged. Auriculoventricular conduction time was increased in four experiments, decreased in six, and unchanged in five. The value of K in Bazett's formula was unchanged in three experiments, decreased in five, and increased in eight. There was no change in respiratory movements until the pH rose above 7.8. The mode of death was ventricular fibrillation or failure of myocardial contractility. The phenomenon of cardiac action currents stimulating somatic nerves was found in three cases.

BERNSTEIN.

Wilens, S. L.: Bearing of General Nutritional State on Atherosclerosis. Arch. Int. Med. 79:129 (Feb.), 1947.

The author points out that in spite of various reports, such as those of French and Dock that overweight and atherosclerosis are definitely connected, other equally definite statements, such as that of Weiss and Minot in 1933, and of Wright in 1943, lead one to believe that "there is no proof that overnutrition leads to atherosclerosis in man."

However, taking his data from 1,000 consecutive autopsies performed in the Bellevue Hospital in New York, and 250 consecutive autopsies on obese persons over the age of 35, Wilens attempts to demonstrate statistically the close relationship between obesity and atherosclerosis.

The series is divided into three groups, according to the state of nutrition as evaluated at autopsy. The statement as to the general state of nutrition recorded in the protocol was generally accepted in making this classification. The author points out that some inaccuracy was unquestionably involved in this method. However, as a general rule, the state of body at necropsy is less likely to show evidence of obesity than at any other time.

The patients of each nutritional group were reclassified by the degree of atherosclerosis present into the following categories: (1) Those with no atherosclerotic lesions anywhere in the arterial system, or only slight ones; (2) those with lesions of moderate degree; and (3) those with severe and widespread lesions. Here again, the pathologist's estimate, as recorded in the protocol, was accepted. The author again admits that such a method is open to criticism.

The statistical analysis of data yielded the following results:

In each sex, atherosclerosis was definitely more marked in the obese group than in the average group, and more marked in the average group than in the poorly nourished group. This was true in the peripheral as well as the coronary arteries. Obese women appeared to have a somewhat lower incidence of severe atherosclerosis than obese men. A similar result again prevailed when the results were analyzed with respect to age, hypertension, heart weight, and the presence or absence of diabetes.

The author concludes that although the analysis is based on the state of nutrition as observed at necropsy, evidence is presented to show that if the analysis had been based on the probable state of nutrition prior to the onset of the final illness, the relationship between atherosclerosis and nutrition would be even more striking.

HORWITZ.

Plotz, M.: Bronchial Spasm in Cardiac Asthma. *Ann. Int. Med.* 26:521 (April), 1947.

On the basis of improvement in the vital capacity which followed within thirty seconds the subcutaneous injection of 0.5 c.c. of a 1:1000 solution of epinephrine in nine cases of heart failure, the author concludes that bronchial constriction, reflexly induced, is the basic difficulty in cases of cardiac failure with so-called "cardiac asthma." By contrast, in eleven cases of severe heart failure with basal pulmonary congestion without wheezing, the administration of this drug did not result in any significant increase in the vital capacity. The author regards as untenable the possibility that the drug ameliorated the symptoms by increasing the heart action, or by decreasing submucosal edema, or by relieving congestion in the interalveolar framework.

WENDKOS.

Seldin, D. W., Kaplan, H. S., and Bunting, H.: Rheumatic Pneumonia. *Ann. Int. Med.* 26:496 (April), 1947.

The clinical, roentgenographic, and pathologic findings in six fatal cases of active rheumatic fever with carditis, complicated by rheumatic pneumonia, are summarized. A uniform clinical picture, characterized by an abrupt onset of profound respiratory distress in the absence of commensurate physical signs in the chest, was encountered in all instances. Hacking cough with scanty, blood-streaked sputum, moderate to high fever, and leucocytosis were also present. In the roentgenogram, the process was manifested by bilateral, multilobar, nonsegmental infiltrations resembling the shadows produced by pulmonary edema.

The histologic lesions could be included in one or more of five categories: (a) an edematous infiltration of the alveolar walls and interstitial tissues ultimately becoming replaced by endothelial cells and fibroblasts; (b) an accumulation of exudate in the alveoli consisting of fibrin, edema, polymorphonuclear leucocytes, mononuclear and multinuclear phagocytic cells ultimately undergoing organization; (c) a hyalinized fibrinous pseudomembrane lining the small bronchioles, believed to be the result of intra-alveolar material being forced upward by inspiratory effort during an attack of dyspnea; (d) vascular lesions in the pulmonary capillaries and arterioles which

ranged from intracapillary hyaline thrombi to intramural and perivascular cellular infiltrations involving the arterioles; and which were subsequently transformed into hyalinization of the intima, scarring of the media, and perivascular fibrosis; and (c) the occasional observation of a parenchymal lesion which resembled the Aschoff body.

WENDKOS.

Welin, S., Hamberger, C. A., and Crafoord, C.: Surgically Removed Foreign Body Embolus in the Pulmonary Artery. J. Thoracic Surg. 15:302 (Oct.), 1946.

The authors report a case of a 21-year-old workshop apprentice who was sent to the otolaryngologic clinic with the diagnosis of foreign body in the left lung. He gave the following history: a splinter from an iron wedge had struck him and entered the left groin. An aneurysm developed, for which an operation was performed. Since then he had occasional pain and swelling in the left leg and phlebography showed a defective reflux from that leg. About a year later the patient was referred to the medical clinic with the diagnosis of incipient pneumonia. Roentgen examination at this time disclosed a small bronchopneumonic-like induration with atelectasis at the base of the left inferior lobe and behind the heart. In the bronchus situated in the posterior basal part of the left inferior lobe, about 7 cm. distal to the carina, a very dense, irregularly-shaped foreign body, nearly 1 cm. in length, over 1 mm. in thickness, and from 7 to 8 mm. in breadth, was also revealed. During bronchoscopy a sound and extractor were inserted in the left bronchial branch, but failed to remove the foreign body. The patient was finally operated upon and it was found that the foreign body was fastened in the part of the artery wall adjacent to the bronchus. The foreign body was removed without any complications. There were no clinical or roentgenologic signs of a disturbance of the circulation in the inferior lobe of the left lung, which indicated that no thrombosis developed in the open pulmonary artery.

The authors point out that the foreign body had entered the femoral vein and had been thrown by the blood stream into the pulmonary artery. The ordinary x-ray examination failed to show the position of the foreign body in relation to the bronchial tree, and bronchoscopy alone did not clear up the matter. Location of the foreign body was only made possible through the combination of these two methods.

They report this to be the first case where the diagnosis of foreign body embolus in the pulmonary artery has been made prior to operation and where the foreign body had afterward been extracted by thoracotomy plus arteriotomy followed by vascular suture.

BELLET.

Shumacker, H. B., Jr., and Abramson, D. I.: Sympathectomy in Trench Foot. Ann. Surg. 125:203 (Feb.), 1947.

The authors describe trench foot as a syndrome which follows prolonged exposure of the foot to a wet and cold environment. Physiologic and pathologic alterations may lead to necrosis of tissue in extreme instances and damage to muscles and nerves may occur, followed by fibrosis, atrophy, contractures, sensory disturbances, and pain on weightbearing. Intense vasospasm, noted initially, may be replaced by a transient period of hyperemia and later followed by a return of excessive tonus which persists.

Of 700 patients admitted to the hospital with trench foot, forty-nine were subjected to sympathectomy (removal of the second and third lumbar ganglia with the intervening chain) involving sixty-six lower extremities. Three main groups were analyzed: (1) those with extensive gangrene; (2) those with excessive sympathetic tonus; and (3) those with the complaint of pain on weightbearing.

The results showed that sympathectomy had a favorable effect on the acceleration of the rate of healing of lesions in patients with extensive gangrene associated with vasospasm. It was also useful in treating maceration of skin and secondary infections resulting from prolonged hyperhidrosis. Sympathectomy reduced the severity of symptoms in patients suffering from cold sensitivity, but produced variable results in the treatment of pain due to weightbearing.

LORD.

Addari, F., de Carolis, D., Montevocchi, M., Foscarini, M., Curti, A., Sita, A., Altanta, G., Josonni, D., Rizzo, S., Tavoschi, F., Magoro, G., and Grandi, F.: Clinical and Experimental Studies of Sympathomimetic Compounds (Sympatol, Veritol, Sympamina), Part 1 to 13. *Folia Cardiologica* 5:198 (August), 1946.

In forty normal subjects given the three sympathomimetic substances orally, intramuscularly, or by vein, bradycardia was noted preceding the maximum rise in blood pressure. This was striking with Sympatol and Veritol and is blamed partly on a secondary vagal effect caused by the rise in arterial pressure and partly on a direct action of the substances on heart muscle. Following Sympatol and Veritol, the arterial blood pressure rose in all instances as the result of both an increased cardiac output and peripheral vascular constriction. Rise in pressure after the administration of Sympamina occurred apparently exclusively on the basis of peripheral vasoconstriction. Oscillometric indices increased, especially following Veritol. Venous pressures were found to rise, which was particularly striking upon the administration of Sympamina. A preliminary fall in venous pressure was often noted.

No striking electrocardiographic changes were present after Sympamina. Sympatol caused prolongation of Q-T interval, extrasystoles, nodal rhythms, and occasional prolongation of A-V conduction. In one instance, transient auricular fibrillation was noted. Similar changes may be induced by Veritol and resembled the effects of intravenously injected epinephrine or a combination of sympathetic and parasympathetic compounds. Phonocardiograms revealed a regular increase in the intensity of all heart sounds suggesting a positive inotropic effect exerted by these agents.

Sympatol and Sympamina caused a definite increase in circulating blood volume (method not given) as the result of peripheral vasoconstriction (spleen), while the administration of Veritol was followed by a diminution of blood volume due to pulmonary congestion.

Cardiac output, determined by gas analytic methods and by the pulse volume curves of Boeger and Wetzler, revealed a constant increase with all three substances but was most pronounced following the administration of Sympatol. Sympatol and Veritol increased cardiac output by a direct positive inotropic action on the heart muscle, Sympamina accomplished this by increased cardiac filling secondary to peripheral venous constriction. Oxygen consumption appeared to be increased with all three compounds. Changes in the dynamics of the arterial system were investigated by the use of the sphygmographic analysis of Wetzler and Boeger. Based on measurements of pulse velocity, Veritol constricts the central arterial system (aorta and large vessels), more so than Sympamina and Sympatol. Peripheral resistance appeared to be decreased following Sympatol. This is caused perhaps by splanchnic dilatation overbalancing the effects of vasoconstriction induced in cutaneous areas. Peripheral resistance is greatly increased following the administration of Veritol and Sympamina, which suggests a more diffuse arteriolar constriction. Increase in arterial tension caused by Sympatol, therefore, is assumed to be the result of increased cardiac output, that following Veritol and Sympamina must be considered as a combination of central and peripheral effects.

Red blood cell counts and hemoglobin values rose after the administration of all three agents. Increase in total leucocytes with relative lymphocytosis was commonly observed but occurred particularly after the administration of Sympamina. Increase in red cell count and hemoglobin values are explained by the emptying of blood depots; rise in leucocytes, by contraction of the spleen.

Blood glucose levels rose in response to Sympatol and Sympamina but not following the administration of Veritol. The rise is explained partly by excessive glycogenolysis from the liver and partly by decreased absorption of glucose from the constricted capillaries.

Sympatol administration was followed by but little change in urinary volume, but caused a constant increase in glomerular filtration (creatinine clearance) and in tubular reabsorption (glomerular filtration minus urine volume). Veritol caused diuresis by an increase in glomerular filtration. A similar diuretic effect of Sympamina appeared as the result of decreased tubular reabsorption without striking alteration in glomerular filtration.

Constriction of capillaries was noted together with a long lasting increase in capillary pressure following the administration of all compounds (method of Salvio).

No striking alterations were noted in spinal fluid pressures. The rise following bilateral pressure on the jugular veins was diminished following the administration of these compounds (general vasoconstriction).

Topical application of all compounds caused mydriasis. This was particularly striking following the instillation of Verkol (0.5 per cent solution).

HECHT.

Carlgren, L. E.: Gallop Rhythm in Children Studied by Means of Calibrated Phonocardiography. *Acta paediat.* 33: Suppl. 6, 1946.

A review of the etiology and characteristics of third heart sounds, auricular sounds, and various types of gallop rhythms is presented. The view is expressed that the third sound is caused by vibrations of the ventricular wall secondary to the rapid rush of blood into the ventricle during early diastole. The auricular sounds are presumed to be formed by vibrations of both the ventricular muscle and the atrioventricular valves. An attempt is made to separate the normal third heart sound from protodiastolic gallop rhythm, and the normal auricular sound from an auricular gallop by the use of Mannheim's "calibrated" phonocardiograph. This instrument transmits the response of the recording microphone through various selective high and low pass filters to four oscillograph coils. A series of different frequency bands of heart sounds or murmurs may thus be recorded by separate channels simultaneously. The units are selective for frequency ranges of 0 to 175, 160 to 250, 175 to 400, and 250 to 1,000 cycles per second respectively.

In children, the normal third heart sounds and the auricular sounds are of low voltage and display frequencies below 100 oscillations per second. Gallop rhythms occurring during the same phase of the cardiac cycle reveal greater amplitudes and have frequencies considerably above 100 cycles. Using these criteria, gallop rhythm was recognized in 104 children. Seventy-eight revealed protodiastolic gallop rhythms: two, auricular gallop; and twenty-four were classified as presenting a summation type of gallop. In sixty-four of these children no apparent heart disease was present, but in one-half of these myocardial damage could not be ruled out with certainty. Gallop rhythms of this type were frequently found in acute rheumatic fever but occurred only five times in 300 instances of congenital heart disease.

Gallop rhythms occurred in rabbits four to six days following the injection of caffeine (0.25 Gm. per kilogram) and 0.2 mg. of epinephrine intravenously (Fleisher and Loeb). Myocardial lesions were thus produced in twenty-three of thirty rabbits and gallop rhythms were present in sixteen of the twenty-three animals. It was always found to be associated with excessive cardiac dilatation as demonstrated by x-ray. This favors the concept that a diminished tone of myocardial muscle is a prerequisite for the gallop rhythms.

HECHT.

Mugno, G.: Intraventricular Conduction on Exercise: A Cardiac Function Test. *Folia Cardiologica* 5:439 (August), 1946.

A method previously reported by Pachioli has been employed in which the duration of the QRS complex is measured before and after exercise (step test). The QRS complex before and after the test was enlarged and its duration measured with an accurate comparator. In ten normal individuals and in ten patients with cardiac neurosis a slight decrease in the width of QRS was noted, the degree being directly proportional to the increase in heart rate. Patients suffering from a variety of organic diseases of the heart revealed a prolongation of QRS in most instances. The test is claimed to be of value in cases where organic heart disease is suspected in the face of normal electrocardiographic or roentgenographic findings at rest.

HECHT.

Gregersen, Mangus L. and Root, Walter S.: Experimental Traumatic Shock Produced by Muscle Contusion With a Note on the Effects of Bullet Wounds. A Study of the Clinical Signs of Shock in the Dog and of the Role of Blood Volume Reduction in the Development of the Shock Syndrome. *Am. J. Physiol.* 142:68 (Jan.), 1947.

Experimental traumatic shock was produced in thirty dogs by uniform contusion of the thigh muscles on the anesthetized animal. Only one dog failed to show the characteristic signs of shock.

These signs consisted of the following: (1) fall in blood pressure; (2) tachycardia; (3) fall in rectal temperature; (4) signs of peripheral vasoconstriction, (a) cold extremities (progressive), (b) dry, lifeless appearance of the oral mucous membranes, (c) disappearance from view of the superficial veins; (5) evidence of thirst and vomiting after taking fluids while in shock; (6) central nervous system depression; (7) decrease in plasma volume (35 per cent or greater); and (8) hemoconcentration. Although this report was concerned only with observations made on thirty animals, subsequent investigations carried out in the same laboratory on many other traumatized dogs have confirmed in every respect the results noted.

Muscle trauma which was severe enough to reduce the blood volume by 30 per cent or more invariably produced shock, and the shock was usually fatal. The blood volume was reduced at, or shortly after, injury and remained unchanged for several hours. The loss of fluid occurred only into the injured area and was fully accounted for by the decrease in blood volume and mobilization of fluid from uninjured areas.

These results, supported by subsequent investigations, refute the concept, at one time widely accepted, that the fundamental cause of shock is a general increase in capillary leakage.
BERNSTEIN.

Wang, S. C., Painter, E. E., and Overman, R. R.: The Mechanism of Prolonged Fluorescein Circulation Time in Experimental Traumatic Shock. *Am. J. Physiol.* 148:69 (Jan.), 1947.

Reliable evidence previously reported by the authors indicates that changes in fluorescein circulation time can be used as a simple prognostic index of the condition of dogs after muscle trauma. The fluorescein circulation time showed a gradual increase during the period of incipient shock in those animals which eventually died. In contrast to this progressive increase, simultaneously determined cyanide circulation time increased to a value which was maintained at a plateau until the mean blood pressure fell below 50 mm. Hg when it underwent a further increase. To determine the mechanism of the discrepancy just noted, bilateral upper thoracic sympathectomies were performed on eleven dogs under intravenous nembutal anesthesia, followed in five to seven weeks by trauma to produce shock. On the day before these trauma experiments, control circulation time and plasma volume were determined.

Since the control fluorescein circulation time was only one or, at most, two seconds longer than the control cyanide time, the increasing difference between the two methods in shock must be accounted for by some factor other than the greater distance involved in the measurement by fluorescein. The discrepancy between the two methods indicates a progressive impairment of the peripheral systemic circulatory apparatus in traumatic shock, which is revealed only by the fluorescein method.

In the dogs subjected to sympathectomies, the fluorescein circulation time following trauma behaved in the same manner as did the cyanide circulation time in the normal traumatized animals. These facts indicate that the mechanism of the prolongation of fluorescein circulation time in the normal dog in traumatic shock is associated with an increased activity of the sympathetic nervous system, particularly upon the peripheral portion of the vascular tree.

BERNSTEIN.

Young, R. D., and Hunter, W. C.: Primary Myxoma of the Left Ventricle With Embolic Occlusion of the Abdominal Aorta and Renal Arteries. *Arch. Path.* 43:86 (Jan.), 1947.

The authors report a case of primary tumor of the heart originating in the left ventricle. The patient, a 10-year-old white girl, had a previous history of recurring attacks of tonsillitis and of joint pains. The latter first appeared at the age of 5 years, and one year later a cardiac lesion was discovered.

The final illness was ushered in with leg pains, fever, and convulsions. Cardiac examination revealed a systolic thrill at the apex. Systolic murmurs were heard in both mitral and aortic areas, and there was also a diastolic aortic murmur. The spinal fluid pressure was increased but

the fluid was clear and there was no cell increase. Facial edema developed on the first day of hospitalization. There was anuria, and a catheter obtained only a few c.c. of bloody urine. The blood pressure was 150/84. Under sedation, the convulsions stopped but the anuria continued, as did hypertension and azotemia. The child died on the fifth day with uremia.

Necropsy, which did not include brain examination, showed an enlarged heart, thickened aortic leaflets, and a hypertrophied left ventricle. The latter contained multiple polypoid masses which almost filled the chamber, the largest being 5 x 3 x 2 centimeters. Most of these masses were soft and yellow, and all of them firmly attached to and springing from the wall of the ventricle by a common pedicle. The largest mass extended through the orifice of the aortic valve. A broken-off stump of a pedicle indicated the previous presence of another polyp which was found lodged in the abdominal aorta, blocking the orifices of both renal arteries and loosely attached by early organizing adhesion. The mass was yellow and spongy, similar to the growth in the left ventricle. The main renal arteries were plugged in their beginning by extension of this intra-aortic mass, and both kidneys were acutely infarcted. Thionine stain showed the cardiac tumor to be a myxoma, and similar structure was found in the aortic and renal embolism.

The case was unusual, insofar as embolic phenomena associated with cardiac tumors are rare. In this case another unusual feature was closure of both renal arteries by the embolism.

GOULEY.

Woll, E., and Vickery, A. L.: Primary Fibrosarcoma of the Heart With a Vertebral Metastasis. Arch. Path. 43:244 (March), 1947.

The authors report an instance of a very rare lesion: primary tumor of the heart with distant metastasis. The patient was a 47-year-old housewife who, in the course of three successive hospitalizations in a period of six months, showed a progressive disability of the right arm featured by numbness of the palm, atrophy of the interosseous and thenar muscles, and severe pain in the right shoulder and arm. The heart, at first of normal size, gradually became enlarged. In the first hospitalization a thrusting apical impulse was associated with a systolic mitral murmur. Later, a diastolic murmur was also heard, and leg edema developed. Clubbing of the fingers was progressively marked. Fever, bloody sputum, and progressive diminution of pulmonary aeration shown by x-ray studies were noted in the last hospitalization. At this time x-ray examination also revealed a loss of bone structure in the transverse process of the first thoracic vertebra, the process being "thin and hollow as if filled with expanding tumor." Death was caused by pulmonary insufficiency secondary to congestive heart failure.

Necropsy revealed almost complete occlusion of the mitral orifice by a yellow, firm, polypoid, somewhat lobulated growth, firmly and broadly attached at its base to the posterior wall of the auricle and to the posterior mitral leaflet. The growth was 4 cm. wide, 2.5 cm. high, and 3 cm. thick at the base. On cross section the growth fused with the endocardium and formed a coarse, paly gray, firm, homogeneous mass. The ventricular surfaces of the leaflets were smooth and glistening. The chorda tendineae were thickened, but not distorted. The other valves were normal. The endocardial surface of the left auricle was thickened and roughened. No other areas of tumor, thrombosis, or scarring were seen in the heart. The coronary vessels were normal. Histology revealed the auricular growth to be a spindle-cell fibrosarcoma. There was no evidence of muscle cell origin, nor was there any evidence of myxoma or angioma. There was microscopic invasion of the adjacent subendocardial tissue.

At the level of the first thoracic vertebra there was an ovoid, smooth mass, 5 cm. in length, 2.5 cm. wide, and 1.5 cm. high, firmly attached to the vertebral column, covering the latter and extending to the right over the attachment of the second rib. The tumor invaded and destroyed the underlying bony tissue and compressed the spinal nerve roots as they came out of the spinal canal. Microscopy showed it to be of the same fibrosarcomatous type as the tumor found in the heart.

The lungs showed evidence of prolonged congestion, sclerotic thickening of the pulmonary artery branches, fresh and old thromboses and pulmonary infarctions, and pulmonary fibrosis, as often seen in mitral stenosis.

The authors believe that the cardiac tumor was primary, since a metastatic tumor is usually multiple and involves the myocardium. In their opinion, it is unlikely that a metastatic lesion derived from the vertebral tumor would lodge in the left side of the heart without involvement of the lung. They state that there is no known case of solitary cardiac metastatic tumor. On the other hand, primary sarcoma of the heart generally originates in the auricular structure and frequently metastasizes to the lungs. This case, however, is the first showing metastatic involvement of the vertebral column.

GOULEY.

Handley, C. A., and Telford, J.: The Effect of Digitalis on the Fluid Distribution of the Body. J. Pharmacol. & Exper. Therap. 89:97 (Jan.), 1947.

Digitalis is known to reduce the blood volume and cardiac output of normal subjects. By measuring the blood volume (dye T 1824) and the extracellular fluid (thiocyanate "space") on dogs before and after digitalization, a further attempt was made to study this finding.

Digitalization produced a constant decrease in plasma volume, rise in extracellular fluid, and rise in the hematocrit. The decrease in plasma volume may be explained by the pooling of blood in the liver and spleen. However, the rise in the hematocrit indicates that there was loss of fluid from the vascular system. The increase in extracellular fluid was far greater than could be accounted for by the escape of fluid from the plasma. Therefore, this extra water must come from the cells.

No explanation of these findings or therapeutic implications were drawn.

GODFREY.

Taylor, R. D., Corcoran, A. C., and Page, I. H.: Menopausal Hypertension: A Critical Study. Am. J. M. Sc. 213:475 (April), 1947.

The female menopause, whether natural or artificial, has long been regarded as a cause of arterial hypertension, and the concept of "menopausal hypertension" has gained wide acceptance. Yet the evidence on which this view is based is largely derived from accumulated impressions rather than systematic study. With this in mind, the authors undertook the care of 200 menopausal women, 179 of whom had been surgically castrated and all of whom desired relief of menopausal symptoms. It was found that arterial hypertension was no more common in this group than in the general population. "Vasomotor instability," as exhibited by "hot flashes," perspiration, and tachycardia, are not necessarily associated with hypertension and their alleviation by estrogens need not affect arterial pressure. The menopause seemed to intensify pre-existing psychoneuroses. Despite severely neurotic behavior, hypertension did not develop within three or more years except in six of the subjects. From these data it is concluded that the relationship of the menopause and hypertension is incidental and loss of ovarian secretion is neither a primary nor a contributory cause of arterial hypertension.

DURANT.

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

OFFICERS

President
DR. ARLIE R. BARNES

Treasurer
SAMUEL HARRELL

President Elect
DR. TINSLEY R. HARRISON

Secretary
DR. HARRY E. UNGERLEIDER

Medical Director
DR. CHARLES A. R. CONNOR

Vice-President
DR. CARL J. WIGGERS

Executive Secretary
DR. H. M. MARVIN

BOARD OF DIRECTORS

*THOMAS I. PARKINSON, Chairman.....	New York City	DR. JOHN D. KEITH.....	Toronto, Can.
DR. EDGAR V. ALLEN.....	Rochester, Minn.	DR. ROBERT L. KING.....	Seattle
*DR. E. COWLES ANDRUS.....	Baltimore	MRS. WENDELL KINNEY.....	Los Angeles
*DR. ARLIE R. BARNES.....	Rochester, Minn.	DR. WILLIAM B. KOUNTZ.....	St. Louis
DR. WILLIAM H. BUNN.....	Youngstown, Ohio	DR. EUGENE M. LANDIS.....	Boston
*DR. GEORGE E. BURCH.....	New Orleans	DR. ROBERT L. LEVY.....	New York City
*S. DEWITT CLOUGH.....	Chicago	DR. H. M. MARVIN.....	New Haven, Conn.
*COLGATE W. DARDEN, JR.....	Charlottesville, Va.	DR. THOMAS M. McMILLAN.....	Philadelphia
DR. CLARENCE E. DE LA CHAPELLE.....	Los Angeles	*ROBERT L. MEHORNAY.....	Kansas City, Mo.
DR. GEORGE K. FENN.....	New York City	*DR. IRVINE H. PAGE.....	Cleveland
DR. MORRIS FISHBEIN.....	Chicago	*DR. JOHN J. SAMPSON.....	San Francisco
RUDOLPH F. HAFFENREFFER.....	Chicago	DR. HOWARD B. SPRAGUE.....	Boston
*SAMUEL HARRELL.....	Providence	DR. EUGENE A. STEAD, JR.....	Durham, N. C.
*DR. TINSLEY R. HARRISON.....	Indianapolis	DR. J. ROSS VEAL.....	Washington, D. C.
ALFRED C. HOWELL.....	Dallas	DR. HARRY E. UNGERLEIDER.....	New York City
*DR. T. DUCKETT JONES.....	Bethel, Conn.	DR. HOWARD F. WEST.....	Los Angeles
DR. LOUIS N. KATZ.....	Boston	DR. CARL J. WIGGERS.....	Cleveland
	Chicago	*DR. IRVING S. WRIGHT.....	New York City

*Executive Committee.

ASSEMBLY

DR. EDGAR V. ALLEN.....	Rochester, Minn.	DR. BERNARD W. LEONARD.....	Washington, D. C.
JAMES ANDERSON.....	Philadelphia	DR. ROBERT L. LEVY.....	New York City
DR. E. COWLES ANDRUS.....	Baltimore	CLARE BOOTHE LUCE.....	Ridgefield, Conn.
DR. GRAHAM ASHER.....	Kansas City, Mo.	DR. HAROLD C. LUETH.....	Omaha
DR. ARLIE R. BARNES.....	Rochester, Minn.	RUTH E. LYNCH.....	Los Angeles
DR. EMMET B. BAY.....	Chicago	DR. LOUIS E. MARTIN.....	Los Angeles
DR. ALFRED BLALOCK.....	Baltimore	DR. H. M. MARVIN.....	New Haven, Conn.
ALVA BRADLEY.....	Cleveland	DR. EDWIN P. MAYNARD, JR.....	Brooklyn
EARLE BROWN.....	Minneapolis	DR. SAMUEL J. MCCLENDON.....	San Diego
DR. LEWIS T. BULLOCK.....	Los Angeles	ALFRED J. MCCOSKER.....	New York City
DR. WILLIAM H. BUNN.....	Youngstown, Ohio	DR. HUGH McCULLOCK.....	St. Louis
DR. GEORGE E. BURCH.....	New Orleans	DR. JOHNSON MCGUIRE.....	Cincinnati
DR. EDWARD W. CANNADY.....	East St. Louis, Ill.	DR. THOMAS M. McMILLAN.....	Philadelphia
HARRY C. CARR.....	Philadelphia	ROBERT L. MEHORNAY.....	Kansas City, Mo.
DR. FRANCIS L. CHAMBERLAIN.....	San Francisco	DR. J. ROSCOE MILLER.....	Chicago
PAUL F. CLARK.....	Boston	RICHARD M. MOSS.....	Belleville, Ill.
S. DEWITT CLOUGH.....	Chicago	DR. E. STERLING NICHOL.....	Miami
DR. WARREN B. COOKSEY.....	Detroit	DR. FRANKLIN R. NUZUM.....	Santa Barbara, Calif.
CHANNING H. COX.....	Boston	DR. IRVINE H. PAGE.....	Cleveland
JAMES A. CUNNINGHAM.....	Chicago	THOMAS I. PARKINSON.....	New York City
COLGATE W. DARDEN, JR.....	Charlottesville, Va.	DR. MYRON PRINZMETAL.....	Los Angeles
JUSTIN DART.....	Los Angeles	DR. SAMUEL PROGER.....	Boston
DR. CLARENCE E. DE LA CHAPELLE.....	New York City	DR. DICKINSON W. RICHARDS, JR.....	New York City
DR. GEZA DE TAKATS.....	Chicago	DR. HAROLD H. ROSENBLUM.....	San Francisco
DR. FRANCIS R. DIEUAIDE.....	New York City	DR. PHILIP ROSENBLUM.....	Chicago
DR. HARVEY M. EWING.....	Montclair, N. J.	DR. HOMER P. RUSH.....	Portland, Ore.
DR. GEORGE K. FENN.....	Chicago	DR. JOHN J. SAMPSON.....	San Francisco
RICHARD J. FINNEGAN.....	Chicago	DR. FRANCIS T. SCHWENTKER.....	Baltimore
DR. MORRIS FISHBEIN.....	Chicago	DR. HAROLD N. SEGALL.....	Montreal, Can.
DR. NORMAN E. FREEMAN.....	San Francisco	DR. ARTHUR SELZER.....	San Francisco
ARTEMUS L. GATES.....	New York City	DR. M. J. SHAPIRO.....	Minneapolis
SAMUEL GOLDWYN.....	Los Angeles	DR. HOWARD B. SPRAGUE.....	Boston
A. E. GRAUER.....	Vancouver, B. C., Can.	DR. ISAAC STARR.....	Philadelphia
DR. JAMES A. GREENE.....	Houston	HAROLD E. STASSEN.....	St. Paul
RUDOLPH F. HAFFENREFFER.....	Providence	DR. EUGENE A. STEAD, JR.....	Durham, N. C.
SAMUEL HARRELL.....	Indianapolis	DR. ERNEST L. STEBBINS.....	Baltimore
RICHARD F. HARRISON.....	Syracuse, N. Y.	DR. WILLIAM D. STROUD.....	Philadelphia
DR. TINSLEY R. HARRISON.....	Dallas	DR. HOMER F. SWIFT.....	New York City
DR. JOHN HEPBURN.....	Toronto, Can.	DR. ALEXANDER W. TERRELL.....	Dallas
DR. GEORGE R. HERRMANN.....	Galveston	DR. WILLIAM P. THOMPSON.....	Los Angeles
DR. J. G. FRED HISS.....	Syracuse, N. Y.	DR. HARRY E. UNGERLEIDER.....	New York City
ALFRED C. HOWELL.....	Bethel, Conn.	DR. J. ROSS VEAL.....	Washington, D. C.
DR. W. C. HUEPER.....	New York City	DR. LOUIS E. VIKO.....	Salt Lake City
COLEMAN JENNINGS.....	Washington, D. C.	DR. MAURICE VISSCHER.....	Minneapolis
DR. T. DUCKETT JONES.....	Boston	JOE E. WERTHAN.....	Nashville
DR. ALBERT D. KAISER.....	Rochester, N. Y.	DR. HOWARD F. WEST.....	Los Angeles
DR. LOUIS N. KATZ.....	Chicago	DR. PAUL D. WHITE.....	Boston
SAMUEL H. KAUFFMANN.....	Washington, D. C.	CARL WHITMORE.....	New York City
DR. JEROME G. KAUFMAN.....	Newark, N. J.	DR. CARL J. WIGGERS.....	Cleveland
DR. JOHN D. KEITH.....	Toronto, Can.	DR. FRANK N. WILSON.....	Ann Arbor
DR. ROBERT L. KING.....	Seattle	DR. J. EDWIN WOOD, JR.....	Charlottesville, Va.
MRS. WENDELL KINNEY.....	Los Angeles	GUS S. WORTHAM.....	Houston
DR. WILLIAM B. KOUNTZ.....	St. Louis	DR. IRVING S. WRIGHT.....	New York City
DR. CHESTER M. KURTZ.....	Madison, Wis.	J. D. ZELLERBACH.....	San Francisco
DR. EUGENE M. LANDIS.....	Boston		

MEMBERSHIP

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members resident in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....	\$ 2.50	Contributing Membership.....	\$25.00
Journal Membership.....	\$10.00	Patron Membership.....	\$50.00 or more
The dues of the local Heart Associations are added to these.			

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*.

Journal Membership includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the AMERICAN HEART JOURNAL through the publishers does not provide for membership in the American Heart Association.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 34

OCTOBER, 1947

No. 4

Original Communications

ANEURYSM OF THE PULMONARY ARTERY: REVIEW OF THE LITERATURE AND REPORT OF A CASE

RALPH A. DETERLING, JR., M.D.,* AND O. THERON CLAGETT, M.D.†
ROCHESTER, MINN.

TRUE aneurysm of the pulmonary arterial trunk or of its major branches, whether the aneurysm is saccular or fusiform, deserves to be listed with the rare lesions of the vascular system. A review of some reported series of necropsies bears this out.

FREQUENCY OF OCCURRENCE

In Table I it is seen that in a group of 109,571 post-mortem examinations aneurysm of the pulmonary artery has been encountered and described only eight times. This is a ratio of one case in 13,696 necropsies. Similarly, various authors reporting large series of arterial aneurysms, even when those lesions are restricted to intrathoracic vessels, only rarely find an aneurysm of the pulmonary artery (Table II). In the English literature, from 1785 to 1847, Crisp¹⁷ found only two cases among 530 aneurysms. In 1910 Giroux,²⁵ in reviewing 116 mediastinal aneurysms, found only one case of dilatation of the pulmonary artery with atherosclerosis. In 1918 Nikolaiew⁶⁵ studied 271 cases of mediastinal aneurysm and described two pulmonary arterial aneurysms, only one of which, however, was confirmed by necropsy. In a total of 1,671 cases of aneurysm compiled by Lucke and Rea⁵⁹ in 1921, Klotz⁴⁷ in 1926, and Scott⁹¹ in 1934, there were no pulmonary aneurysms. Blakemore, in a recent letter to the authors, indicated that there were no aneurysms of the pulmonary artery among the 456 aneurysms seen at Presbyterian Hospital in New York City between 1917 and 1936. Such also was the case when Mills and Horton⁶³ in 1938 reviewed 596 arterial aneurysms, of which 339 were intrathoracic, seen at the Mayo Clinic from 1925 to 1935.

Received for publication Dec. 28, 1946.

*Fellow in Surgery, Mayo Foundation.

†Division of Surgery, Mayo Clinic.

We recently studied the records of 146 patients seen at the Mayo Clinic in the past eleven years, concerning whom a definite clinical diagnosis of mediastinal aneurysm had been made, without the finding of one aneurysm of the pulmonary artery.

TABLE I. ANEURYSMS OF THE PULMONARY ARTERY IN NECROPSY MATERIAL, 1848 TO 1946

AUTHORS	NECROPSIES, NUMBER	ANEURYSM, CASES	YEARS	PLACE
Dlauhy ²¹	10,000	1	1848	
Scott ²¹	13,234	0	1867-1912	St. Bartholomew
New York City ²¹	10,000	0	1918-1924	
Costa ¹⁶	20,000	1	1929	Institute of Florence
Käppeli ⁴²	8,000	1		
D'Aunoy and von Haam ¹⁹	11,377*	2	1906-1934	Charity, New Orleans
Jennes ³⁵	14,523	2	Up to 1936	Johns Hopkins
Sisson, Murphy, and Newman ²²	4,892	0	1936-1945	Johns Hopkins
Deterling and Clagett	17,545	1	1910-1946	Mayo Clinic
Totals	109,571	8		

*The number of necropsies involved in the series of D'Aunoy and von Haam was not disclosed in their paper. It was kindly furnished to the present authors on Aug. 19, 1946, by Dr. Emma S. Moss, director of the Department of Pathology of the Charity Hospital of Louisiana at New Orleans.

TABLE II. THE OCCURRENCE OF ANEURYSM OF THE PULMONARY ARTERY AMONG ALL REPORTED ANEURYSMS OF INTRATHORACIC VESSELS, 1785 TO 1946

AUTHORS	VARIOUS ANEURYSMS, TYPES AND NUMBER	ANEURYSMS OF PULMONARY ARTERY, NUMBER	YEARS	PLACE
Crisp ¹⁷	530 total	2	1785-1847	England
Giroux ²⁵	116 mediastinal	1	1910	France
Nikolaiew ²⁵	271 mediastinal	2	1918	Russia
Lucke and Rea ³⁷ Klotz ¹⁷ Scott ³¹	1,671 total	0	1921 1926 1934	
Blakemore	456 total	0	1917-1936	New York
Mills and Horton ⁴²	596 total 339 thoracic	0	1925-1935	Mayo Clinic
Deterling and Clagett	147 mediastinal	1	1935-1946	Mayo Clinic
Totals	4,126	6		

CRITERIA FOR CLASSIFICATION

The importance of setting up definite criteria for proper classification of lesions of the pulmonary artery has been emphasized by Boyd and McGavack.⁷ In accord with the qualifications they set forth and with the definitions in the leading textbooks of pathology, we have accepted as authentic instances only those in which, at necropsy, a permanent, more or less circumscribed dilatation of the pulmonary artery with some organic degeneration of its wall could be demonstrated (Table III). Listed separately are a series of twenty-three cases in which an unproved clinical diagnosis alone was reported (Table IV).

Early in our search of the literature, we were impressed with the extreme difficulty of determining whether many instances of definite and sizable dilatation of the pulmonary artery should be considered as examples of aneurysm. Although previous authors included patients concerning whom a clinical diagnosis of aneurysm of the pulmonary artery had been made, we were not convinced that there existed a justifiable basis for the diagnosis in many of the histories we reviewed. Further evidence for viewing the clinical diagnosis with some skepticism in a statistical analysis such as this was furnished by the number of published necropsy reports concerning patients in whom marked dilatation of the pulmonary artery had existed during life, but in whom no significant alterations of the wall of the vessel could be found histologically. Thompson⁹⁹ showed by angiography and surgical exploration that in two cases in which the diagnosis was "pulmonary aneurysm" the true lesions were aortic aneurysm and a bronchiogenic carcinoma of the lung. Dilatation of the pulmonary artery was a surprisingly frequent finding, but since one must have proof of destruction of one or more layers of the wall of the vessel before one can describe a lesion accurately as "aneurysm," we have been forced to accept only those cases in which the observations made at necropsy were compatible with the definition. Since we are interested only in aneurysm of the trunk or primary branches of the pulmonary artery, we have also excluded all instances of simple dilatation or aneurysm of the small peripheral branches.

Among the latter, the Rasmussen aneurysm of a peripheral artery in the wall of chronic tuberculous cavities is said to be found in 4 to 5 per cent of necropsies of patients who die of chronic pulmonary tuberculosis.^{4,33} West¹⁰⁴ said that Rokitsky had a case in which this condition was associated with massive cavitation of the lung. Between the years 1877 and 1884, West¹⁰³⁻¹⁰⁶ himself reported six instances of aneurysm of the pulmonary artery, but these were found to be associated with tuberculous cavities. Similarly, Kidd⁴⁵ in 1884 reported four cases of Rasmussen aneurysm. This author found twenty-six aneurysms of the pulmonary artery in 230 persons who died of pulmonary tuberculosis. Sixty-five per cent of these persons died of rupture of the sac and fatal hemorrhage. Auerbach⁴ described forty-five cases from among 1,114 necropsies of people who had died of chronic pulmonary tuberculosis.

A number of cases have been excluded from the present paper because of aneurysmal involvement of only secondary or peripheral branches of the vessel in question. West¹⁰³ in 1877 reported on a woman 46 years of age who died of

TABLE III. SALIENT DATA IN THIRTY-SIX CASES OF ANEURYSM OF THE PULMONARY ARTERY PROVED AT NECROPSY

No.	YEAR	REPORTED BY	PATIENT		ANEURYSM, TYPE, AND SITE	ORIGIN	CLINICAL FINDINGS	POST-MORTEM DATA
			AGE	SEX				
1	1860	Bristowe ¹⁰	59	M	Fusiform, trunk	Atheroma	Cough, hemoptysis, epistaxis, edema, ascites	Hypertrophy right heart, atheroma pulmonary artery, aorta normal
2	1893	Hebb ¹¹	40	M	Saccular, trunk, and right artery	Atheroma Congenital?	Cough, hemoptysis, dyspnea, murmur, and thrill	Atheroma of pulmonary artery and aorta; aneurysm, size of turkey egg. Ductus arteriosus with aneurysm size of walnut; cardiac hypertrophy
3	1917	Winternitz and Schmeisser ¹¹⁶	56	M	Saccular, right*	Syphilis?	Short of breath, edema, ascites, test for syphilis negative	Fibrosis of lungs, chronic pleuritis, aneurysm right pulmonary artery with mesarteritis, right ventricle dilated and hypertrophic
4	1918	Nikolaiew ⁴⁵	?	?	Fusiform, bilateral	?	Dyspnea, hemoptysis, test for syphilis negative	Cardiac hypertrophy. Aorta normal
5	1920	Wildhagen ¹⁰⁷	?	?	Saccular? Left	Mycotic		Endocarditis, mitral and aortic valvular ulcerations. Large aneurysm left pulmonary artery. 1 small peripheral aneurysm in lower left lobe. Streptococcus found
6	1921	Ribierre and Giroux ³³	67	F	Fusiform, trunk	Atheroma	Dyspnea, cough, late cyanosis, edema and ascites, heart enlarged, murmur and thrill, right axis deviation, polycythemia, test for syphilis negative	Marked sclerosis with dilatation; diffuse arteriosclerosis
7	1927	Laubry and Thomas ³²	38	M	Fusiform, trunk	Syphilis	Dyspnea, hemoptysis, cyanosis, tachycardia, hemothorax, test for syphilis 3+	Right heart dilated, aneurysm pulmonary artery. Infarction right middle lobe
8	1927	Laubry and Thomas ³²	45	F	Saccular, trunk	Syphilis	Dyspnea, cough, hemoptysis, cyanosis, edema; liver and heart enlarged; murmur and thrill, right axis deviation; test for syphilis 3+	Aneurysm, sac 6 cm., fibrous pulmonary tuberculosis

927	Laubry and Thomas ⁵²	59	F	Fusiform, trunk	Syphilis	Dyspnea, edema, cyanosis, test for syphilis 4 +	Enormous dilatation pulmonary artery
10	1927	62	M	Fusiform, trunk	Syphilis	Dyspnea, edema, cyanosis, hemoptysis, test for syphilis 3 +	Enormous dilatation right heart dilated
11	1927	38	M	Fusiform, trunk	Syphilis	Dyspnea, cyanosis, acute pulmonary edema	Marked dilatation pulmonary artery
12	1930	59	F	Fusiform, trunk	Syphilis	Dyspnea, edema, aortic valvular disease, test for syphilis 3 +	Fusiform dilatation pulmonary artery (9 cm. diameter). Heart dilated and hypertrophic (460 Gm.); valves syphilitic
13	1930	28	F	Fusiform, trunk	Syphilis	Dyspnea, heart enlarged, murmur and thrill; tachycardia, hypertension; test for syphilis negative	Marked dilatation pulmonary artery (12 cm. circumference); Döhle-Heller type aortitis; chronic nephritis
14	1933	36	F	Saccular, trunk	Congenital, mycotic	Fever, cough, dyspnea, edema, cyanosis, anemia	Aneurysm anterior wall 3 by 2.5 cm.; ductus arteriosus 4 mm. diameter. Healed endarteritis, thrombus 3.5 by 2.5 cm. with streptococci. Fibrinous pericarditis. Chronic nephritis
15	1933	30	M	Fusiform, trunk	Syphilis	No symptoms. Right axis deviation. X-ray positive; aorta normal	Moderate dilation pulmonary artery
16	1934	44	M	Saccular, trunk	Syphilis	Edema, dyspnea, cough, cyanosis, test for syphilis 3 +	Aneurysm with syphilis microscopically. Aorta fairly free, right heart hypertrophic
17	1938	58	F	Fusiform, bilateral	Syphilis? Suppurative pulmonary disease	Dyspnea, faint, no murmur	Heart enlarged, pulmonary artery dilated; 18 cm. circumference. Pulmonary ring 12 cm. circumference
18	1939	44	M	Saccular, trunk, and multiple peripheral vessels	Congenital, mycotic	Machinery murmur, subacute bacterial endocarditis after dental extraction with positive culture. Late chest pain	Pulmonary artery dilated, with mycotic sac lateral wall (4 cm.). Multiple peripheral mycotic aneurysms from few mm. to 3 cm. in size. Ductus arteriosus 1.5 cm. with calcification. Right heart enlarged. Fibrinous pericarditis

TABLE III. SALIENT DATA IN THIRTY-SIX CASES OF ANEURYSM OF THE PULMONARY ARTERY PROVED AT NECROPSY—(CONT'D)

NO.	YEAR	REPORTED BY	PATIENT		ANEURYSM, TYPE, AND SITE	ORIGIN	CLINICAL FINDINGS	POST-MORTEM DATA
			AGE	SEX				
19	1939	Bello ³	44	M	Fusiform, trunk	Syphilis	Hemoptysis, dyspnea, chest pain, slight cyanosis; murmur; test for syphilis 3 +	Pulmonary syphilitic arteritis, 12.5 cm. circumference. Right heart hypertrophic. Tricuspid insufficiency. Mitral stenosis. Diffuse arteriosclerosis
20	1939	Duperie and de Lachaud ²²	40	F	Fusiform, trunk	Atheroma	Right heart failure, marked cyanosis, dyspnea, liver enlarged, edema. Sudden death	Pulmonary artery dilated with split in posterior wall, rupture into pericardium. Right heart dilated and hypertrophic; aorta normal, diffuse arteriosclerosis. No infarction
21	1940	Wilkinson ^{10a}	10	F	Fusiform, right	Congenital	Scoliosis, systolic murmur, severe pain at terminal rupture	Aneurysm pulmonary artery, 3 inches. Interventricular septal defect. Aortic hypoplasia. Bicuspid pulmonary valves
22	1940	Allan and McCracken ¹	54	F*	Fusiform, trunk	Syphilis	Cough, dyspnea, late edema, and cyanosis. Murmur and thrill, heart enlarged, right axis deviation, test for syphilis 4 +	Pulmonary artery 15 cm. circumference. Cardiac hypertrophy. Syphilitic arteritis
23	1941	Laubry and Routier ²¹	36	F	Fusiform, trunk	Atheroma Congenital?	Cyanosis, murmur, later edema; red blood cells 5,180,000 per cubic millimeter, electrocardiogram, right axis. X-ray positive	Right ventricle enlarged, pulmonary artery dilated (circumference 9 cm.) with atheroma. Single pulmonary infarct, no septal defect
24	1941	Laubry and Routier ²¹	35	M	Fusiform, trunk	Atheroma Congenital?	Cough, slight cyanosis, murmur. Red blood cells 5,440,000 per cubic millimeter, electrocardiogram right axis, x-ray positive. Late edema and ascites	Heart enlarged on right, pulmonary artery dilated (circumference 10 cm.) with atheroma, no septal defect. Mitral "est inserée sur trois piliers"

1941	Laubry and Routier ⁵¹	34	M	Fusiform, trunk	Atheroma Congenital?	Cyanosis, cough, dyspnea, occasional edema, murmur and thrill; x-ray positive; electrocardiogram right bundle branch block	Heart, 650 Gm.; right heart enlarged. Pulmonary artery diameter 2 times aorta, with atheroma, no septal defect
26	Laubry and Routier ⁵¹	47	M	Fusiform, trunk and branches	Atheroma Congenital?	Cough, dyspnea, cyanosis, murmur, x-ray positive, electrocardiogram right bundle branch block	Heart enlarged on right, left side small; aorta small; pulmonary artery enormous with atheroma and dissection. Interventricular defect 5 cm. in diameter
27	Laubry and Routier ⁵¹	40	M	Fusiform, trunk and branches	Atheroma Congenital?	Fatigue, rheumatism history; murmur third intercostal space, died of subacute bacterial endocarditis. Electrocardiogram, left bundle branch block	Mitral stenosis, small aorta, left heart enlarged, pulmonary artery dilated. with atheroma; no septal defects. Ulcerative vegetation in left ventricle
28	Laubry and Routier ⁵¹	29	M	Fusiform, trunk	Congenital?	Murmur and thrill second intercostal space; slight cough and epistaxis; electrocardiogram, right axis deviation	Right heart enlarged, aortic ring hypoplasia, diameter 2.8 cm.; pulmonary artery 8 centimeters. Small plaques. No septal defects
29	De Navasquez ⁵²	57	M	Saccular, trunk, and left	Syphilis	Dyspnea, late cyanosis, edema and ascites, test for syphilis 4 +	Pulmonary aneurysm 6 by 5 centimeters. Congestive heart failure, pulmonary fibrosis
30	Yuskis ⁵²	21	F	Saccular, right	Congenital	Pain, hemoptysis, murmur, electrocardiogram normal, test for syphilis negative	Pulmonary aneurysm 3 by 4 centimeters. Rupture into bronchus. Ductus arteriosus
31	Johannsen and Connor ⁵²	44	F	Saccular, bilateral	Congenital	Cyanosis, dyspnea, cough, severe hemoptysis, clubbing, heart enlarged, murmur, right axis deviation, polycythemia	Bilateral pulmonary aneurysms; right, 3 cm., left, 2.5 centimeters. Patent ductus arteriosus 1.2 cm. diameter, interventricular septal defect 8 millimeters. Foramen ovale closed. Heart and liver enlarged
32	Hartwell and Tilden ⁵²	12	F	Saccular, trunk	Congenital, mycotic	Heart enlarged, hemoptysis, murmur, subacute bacterial endocarditis with ductus. Two blood cultures positive for streptococci. Sharp pain 2 days ante mortem	Pulmonary aneurysm 3.5 by 2.5 cm. anterior wall (tear 1 cm.). Ductus arteriosus. Mitral vegetation. Heart, spleen, and liver enlarged. Multiple small lung infarcts

TABLE III. SALIENT DATA IN THIRTY-SIX CASES OF ANEURYSM OF THE PULMONARY ARTERY PROVED AT NECROPSY—(CONT'D)

NO.	YEAR	REPORTED BY	PATIENT		ANEURYSM, TYPE, AND SITE	ORIGIN	CLINICAL FINDINGS	POST-MORTEM DATA
			AGE	SEX				
33	1914	Lequime, van Heerswyngheles, and Herlant ⁵⁷	32	F	Fusiform, trunk	Congenital, atheroma	Cyanosis, dyspnea, clubbing, diastolic murmur, heart enlarged; x-ray: dilatation and calcification of pulmonary trunk. Electrocardiogram, right axis deviation. Polycythemia, edema, hemoptysis at end	Heart 650 Gm., hypertrophic right auricle and ventricle. Marked dilatation pulmonary artery with sclerosis. Defect of interauricular and interventricular septa
34	1914	Jouve, Delaage, and Oddo ⁴¹	27	F	Fusiform, trunk and branches	Congenital, mycotic	Dyspnea, tachycardia since 14 years. Murmur and thrill, second and third intercostal spaces; x-ray positive; electrocardiogram negative? Tuberculosis developed; died of rupture into cavity	Heart enlarged, especially right. Dilatation pulmonary trunk (12.5 cm. circumference) and right branch (10 cm.). Aorta normal
35	1914	Lenègre, Roudinesco, and Marquis ⁴⁴	32	M	Fusiform, trunk and branches	Congenital	Cyanosis, clubbing, murmur. X-ray positive. Death from cardiac failure	Heart enlarged. Cor triloculare with transposition of great vessels. Small aorta, large dilated pulmonary artery, with thickened wall and intense diffuse endarteritis
36	1915	Deterling and Clagett†	37	M	Saccular, right	Atheroma Congenital Trauma?	Cough, hemoptysis, later pain, dyspnea, cyanosis, clubbing. Electrocardiogram, right axis deviation. Test for syphilis negative; polycythemia	Right pulmonary aneurysm 3 by 7 cm. (near 1 cm.). Ductus arteriosus 1 cm. diameter. Right cardiac hypertrophy. Marked diffuse arteriosclerosis

*Negro.

†Reported by Scott.²¹

‡Diagnosed clinically and confirmed at necropsy.

rupture of an aneurysm of a branch of the right pulmonary artery, associated with severe bronchiectasis. Kidd⁴⁶ in 1893 presented a case in which a 22-year-old woman had an embolic aneurysm the size of a walnut in a secondary branch of the artery to the lower lobe of the left lung. Wolff-Bremen¹¹¹ in 1936 reported multiple mycotic aneurysms of the secondary branches in a woman 21 years of age who had had angina and polyarthritic rheumatism. Höra and Wendt³⁷ in 1941 saw a patient who had pulmonary thromboendarteritis with multiple mycotic aneurysms. Lelli⁵⁴ in 1941 reported multiple mycotic aneurysms of the pulmonary arteries in the presence of ulcerous endocarditis of the aorta and patent ductus arteriosus. Clausen¹³ in 1945 described the condition of a 69-year-old woman who died of rupture (into a bronchus) of an aneurysm of a peripheral pulmonary artery in the lower lobe of the left lung. Henschen³⁵ in 1945 reported on a 31-year-old man who had suppurative disease of the lung, concerning whom the clinical diagnosis of multiple peripheral dissecting aneurysms and arteriosclerosis of the pulmonary artery had been made.

There have been many reports of cases in which definite dilatation of the pulmonary artery was present, but without evidence of a destructive process of the wall of the vessel. Such lesions could not be classified as aneurysms. Among the cardiovascular conditions causing dilatation of the pulmonary artery are mitral stenosis, primary pulmonary arteriosclerosis,² and certain congenital anomalies. These latter should include particularly (1) interauricular septal defect, (2) patent ductus arteriosus, (3) Lutembacher's complex (interauricular septal defect and mitral stenosis), (4) Eisenmenger's complex (the tetralogy of Fallot in which a dilatation rather than stenosis of the pulmonary artery is present), and (5) unequal division of the truncus arteriosus (the "grosse pulmonaire—petite aorte" of Laubry).^{49,53} In Table V we have outlined the causes of pulmonary arterial dilatation. On reviewing the cases of proved aneurysms, one notes that on the basis of the nature of the underlying lesion, many of the atheromatous aneurysms developed after simple dilatation. This subtle transformation of simple dilatation to actual aneurysm frequently has made it impossible to classify accurately cases in which a clinical diagnosis alone had been made. We felt, therefore, that it was imperative to accept only cases in which the condition had been proved at necropsy if any significant statistical analysis was to be made.

Excluded because of simple dilatation are two cases of Wilks¹⁰⁹ (1860).

The case of Crouzon and Grenaudier¹⁸ (1922) is omitted because the fusiform dilatation was secondary to pressure from tuberculous nodes in the mediastinum.

McGinn and White,⁶² in their review of twenty-four cases of interauricular septal defect, mentioned the marked degree of dilatation of the pulmonary artery seen in some of these patients. Cossio and Arana¹⁵ (1937), in discussing the same lesion, reported three cases in which dilatation was present. Laubry and Routier⁵¹ in 1941 presented data concerning thirty-nine patients personally seen by them who showed the same syndrome as that of interauricular septal defect. Their failure to find a defect in seven of the eight patients who came to necropsy led them to consider malposition of the septum in the fetal truncus

TABLE IV. TWENTY-THREE CASES FROM THE LITERATURE IN WHICH THE DIAGNOSIS OF ANEURYSM OF THE PULMONARY ARTERY WAS MADE CLINICALLY.

NO.	YEAR	REPORTED BY	PATIENT		ANEURYSM, TYPE, AND SITE	ORIGIN	CLINICAL FINDINGS
			AGE	SEX			
1	1920	Laubry and Parvut ⁵⁰	?	F	Fusiform, trunk	Congenital	Dyspnea, tachycardia, late cyanosis, murmur, and thrill. Test for syphilis negative
2	1921	Queyrat, Gandy, and Deguignand ⁷⁹	22	M	Fusiform? Trunk	Congenital?	Weak, palpitation, cough, thrill, and murmur. Congenital syphilis? Test for syphilis negative. Hypertension
3	1924	Arrillaga ³	54	M	Fusiform, trunk	Syphilis. Primary pulmonary sclerosis	Dyspnea, cyanosis, cough. Test for syphilis 4+. Polycythemia
4	1925	Pezzi and Silingardi ⁷⁴	36	F	Fusiform? Trunk	Congenital?	Dyspnea, occasional cyanosis, murmur, and thrill. Right axis deviation
5	1933	Gonzalez-Sabathie ²⁶	29	F	Fusiform? Trunk	Syphilis	Dyspnea, palpitation, pain, slight cyanosis, murmur, right axis deviation. Test for syphilis 4+
6	1933	Gonzalez-Sabathie ²⁶	32	F	Fusiform? Trunk	Syphilis	Dyspnea, dizziness, edema, pain, cyanosis, murmur. Right axis deviation. Test for syphilis positive. Hypertension
7	1933	Gonzalez-Sabathie ²⁶	37	M	Saccular? trunk	Syphilis trauma?	Pain, injury, dyspnea, murmur. Right axis deviation. Test for syphilis positive
8	1935	Gonzalez- Sabathie ^{27,28}	39	F	Saccular, left	?	Dyspnea, dizziness, edema, murmur. Electrocardiogram normal. Test for syphilis negative. Ductus arteriosus?
9	1938	Raynaud, Tillier, and Huguenin ⁸⁰	70	M	Saccular? Trunk	Syphilis? Emphysema	Dyspnea, cough, cyanosis, clubbing, edema. Heart enlarged. Thrill, tachycardia. Hypertension
10	1939	Plencznev ⁷⁶	59	M	Fusiform? Trunk	Congenital?	Dyspnea, cough. Murmur (systolic and diastolic). Ductus arteriosus. Test for syphilis negative. Hypertension. Electrocardiogram right axis deviation
11	1939	Groedel ⁸⁰	42	M	Saccular, left	Trauma?	Injury. No symptoms. Test for syphilis negative

TABLE V. OUTLINE OF CAUSES OF DILATATION OF THE PULMONARY ARTERY

-
- I. Congenital cardiovascular anomalies
 - A. Simple interauricular septal defects
 - B. Patent ductus arteriosus
 - C. Unequal division of the truncus arteriosus communis
("grosse pulmonaire-petite aorte" of Laubry)
 - D. Lutembacher's complex (mitral stenosis and interauricular septal defect)
 - E. Eisenmenger's complex of the tetralogy of Fallot
 - F. Congenital malformation of the arterial wall
 - II. Acquired pulmonary hypertension
 - A. Extravascular
 - 1. Pulmonary fibrosis
 - 2. Infarction
 - 3. Emphysema
 - 4. Benign and malignant tumors of the lung or mediastinum
 - 5. Mediastinal lymphadenopathy
 - 6. Pressure from aortic aneurysm
 - B. Intravascular
 - 1. Mitral stenosis
 - 2. Primary pulmonary arteriosclerosis (Ayerza)
 - 3. Obliterative pulmonary arteriosclerosis
 - 4. Aortopulmonary fistula
 - 5. Peripheral and pulmonary arteriovenous fistula
 - 6. Pulmonary embolism
 - III. Destructive processes of the arterial wall
 - 1. Syphilitic
 - 2. Tuberculous (Rasmussen)
 - 3. Mycotic
 - 4. Atheromatous
 - 5. Traumatic
 - IV. Idiopathic
-

arteriosus as the etiological factor. Such a dilated pulmonary artery and hypoplastic aorta they described as "grosse pulmonaire—petite aorte."⁵³ We recently ligated a patent ductus arteriosus in a girl of 15 years who apparently had this anomaly of the great vessels. Additional cases have been reported by Lenègre and associates,⁵⁵ Routier and Heim de Balsac,⁸⁹ and Soulie and associates.⁹³ Eight cases of idiopathic dilatation were described by Oppenheimer.⁶⁸ Three of the patients concerned came to post-mortem examination, but aneurysmal changes were not recorded. Rundles⁹⁰ in 1945 described the clinical progress of a 56-year-old man who had congenital multiple hemorrhagic telangiectasia. He was believed to have such a lesion in the right lung, and a dilated pulmonary trunk extending from the area to the hilum was referred to as an aneurysm.

A child mentioned by Gibson²⁴ in 1946 had huge dilatation of the pulmonary trunk and branches as a result of primary proliferative arteriosclerosis. No pathologic changes of the main vessel were noted, however.

Equally difficult to separate into distinct categories are certain cases of syphilitic arteritis. Although the pulmonary artery is relatively resistant to this disease, when it is affected an inflammatory destructive lesion of the vessel results. In strict accordance with our criteria, even minimal dilatation in any

case of syphilitic pulmonary arteritis could be classified as aneurysmal, yet we have arbitrarily demanded that moderate alteration of the gross characteristics of such vessels be present before we have added them to the list. Consequently, if permanent dilatation is sufficient, the eleven cases of Karsner⁴³ (1933) may be admitted, but of these the lesion in only three was sharply localized. Of the twelve cases of Laubry and Thomas⁵² (1927), only five were described as involving aneurysmal changes. In Brenner's⁸ comprehensive review of diseases of the pulmonary artery, syphilitic aneurysm was not common. The relatively low pulmonary arterial pressure and large amount of elastic tissue permit more microscopic changes without gross alteration than are seen in the aorta. Furthermore, where both vessels have been involved, death from the aortic aneurysm occurred in some cases before aneurysm developed in the pulmonary vessel. Although Posselt⁷⁸ showed the definite relationship of syphilis to pulmonary aneurysm, the view of Warthin^{101,102} that practically all pulmonary aneurysms are caused by syphilis has been discredited by the studies of Peck,⁷¹ Karsner,⁴³ D'Aunoy and von Haam,¹⁹ and Boyd and McGavack.⁷ In our series of thirty-six cases, syphilis was a possible factor in fourteen (39 per cent), with positive results of serologic studies reported in but ten patients. Similarly, Boyd and McGavack found that syphilis played a possible role in 31.7 per cent of their 139 cases.

A final group of more than twenty cases unfortunately had to be omitted from consideration in the present paper because they were merely mentioned by an author and we were unable to obtain sufficient data to confirm the condition. Romberg's two cases of atheromatous fusiform dilatation of the pulmonary artery were reported briefly by Krzyszkowski⁴⁸ in 1902. Hamilton and Abbott³¹ in 1914 mentioned a case of Gauchery. Nikolaiew⁶⁵ in 1918 simply mentioned one of the two cases in his series of aneurysms. In their report Laubry and Parvu⁵⁰ in 1920 referred to Variot's several instances of dilated pulmonary artery as seen in children who had interventricular septal defects, and to Coyon's case from Trousseau Hospital in which the pulmonary artery had a diameter twice that of the aorta. Reference to a case of aneurysm of the main pulmonary trunk was made by Pissot⁷⁵ in 1920 in her thesis. Thomas⁹⁸ in 1927 had for his subject acquired lesions of the pulmonary artery, and he reported a case of aneurysm. We were unable to find the reports of Desclin (1931) or of Vaquez and Lecomte (1918), both referred to by González-Sabathié²⁶ (1933). Steinberg⁹⁵ in 1933 spoke of a patient seen by Salzer. Robb and Steinberg⁸⁸ mentioned briefly two patients who had what was diagnosed as aortic aneurysm and bronchiogenic carcinoma, respectively, in whom they demonstrated, by angiocardiology, marked dilatation of the pulmonary artery. Laubry and Routier⁵¹ in 1941 tabulated two cases of Schreyer, and five of Kourilsky and Coli, in all of which dilatation of the pulmonary artery secondary to an interauricular septal defect was present. Pérez Simón⁷³ in 1943 mentioned cases of Schutte (1938) and Peña, both reported in Cuban medical literature. Cañedo¹¹ in 1943, in his report of a case, referred to three other patients in his care, all women. In none of his patients was the diagnosis confirmed by necropsy.

Hence, for one reason or another, we have excluded more than 150 cases considered as cases of aneurysms of the pulmonary artery because they did not conform to definite criteria. Reference should be made to the previous series of Henschen,³⁶ Posselt,⁷⁸ Costa,¹⁶ and D'Aunoy and von Haam,¹⁹ as well as to the most recent comprehensive collection of a total series of 139 cases by Boyd and McGavack⁷ in 1939. We shall now present the salient data in thirty-six cases of aneurysm of the pulmonary artery verified by necropsy. A group of twenty-three cases in which only a clinical diagnosis had been made is listed in Table IV. At the end of this section we shall present one case of our own. These data represent a review of the literature up to September, 1946, exclusive of the series reported in 1939 by Boyd and McGavack.

Both reviews then, represent a total of 198 cases, in 147 (thirty-six of this series) of which the diagnosis had been made at necropsy, and in fifty-one (twenty-three of this series) of which the diagnosis had been made by clinical methods and as yet unconfirmed by necropsy. The following statistical analysis will concern only those cases of our series in which the diagnosis was proved by post-mortem examination.

CHARACTERISTICS OF ANEURYSM OF THE PULMONARY ARTERY, VERIFIED AT NECROPSY, AS REPORTED IN THE LITERATURE*

Age and Sex of Patients.—In the thirty-four cases in which the sex of the patient was noted, the relationship of eighteen men to sixteen women is similar to the 1:1 ratio as reported in a series of 108 cases mentioned by Boyd and McGavack.⁷ They pointed out the contrast in the sex distribution of aneurysm of the pulmonary artery in respect to that of aortic aneurysm, in which the ratio greatly favors the male. The average age in the present series was about three years more than that of the entire group studied by Boyd and McGavack. In the thirty-four cases in which the age was noted, we found men to average 42.8 years and women to average 39.3 years. Of the total of 142 patients, composed of thirty-four from our series and 108 from the series of Boyd and McGavack in which age was mentioned, 30 per cent were less than 30 years of age, as compared with the 15 per cent of patients less than 30 years of age when aortic aneurysm is considered.

Location and Type of Lesion.—There have been varying figures as to the prevalence with which the main trunk has been involved primarily. Costa¹⁶ said that such involvement occurred in 85 per cent of cases and Boyd and McGavack⁷ listed such involvement in 80 per cent of cases. In the thirty-six cases which we collected, the trunk was affected, with or without involvement of the major branches, in 89 per cent. In 8 per cent only the right branch was involved, and in 3 per cent the left branch was involved. It has been noted by others that the left branch was the site of aneurysmal dilatation more frequently than the right. The type of aneurysm could be determined in all thirty-six cases; it was fusiform in twenty-four and saccular in twelve. The resultant ratio of 2:1 in

*Including the case we shall report herein.

favor of fusiform aneurysm is at variance with that in Boyd and McGavack's series, in which the ratio of fusiform to saccular aneurysms was 3:4.

Etiological Factors.—

Syphilis: There has been considerable controversy in the past as to the role syphilis plays in the formation of pulmonary aneurysm. Of the 139 cases previously reported by Boyd and McGavack,⁷ syphilis was a positive factor in 31.7 per cent. In the thirty-six cases we collected, the authors indicated that syphilis had played a probable role in 39 per cent. This is in contradiction to the stand taken by Warthin¹⁰¹ in 1917, who thought that in all the cases he had reviewed the lesion was due to syphilis.

Congenital Defect: There seems little doubt that cardiovascular anomalies occur in cases of pulmonary aneurysm much more often than in a control group. The aneurysm was believed to have a congenital basis in 47 per cent (seventeen cases) of the thirty-six cases in the present series in which necropsy had been carried out. Although Boyd and McGavack⁷ found anomalies in 66 per cent of their cases, they considered such anomalies to be important in the etiology in 43.2 per cent of cases. In both the present series and that of Boyd and McGavack, by far more patients had a patent ductus arteriosus than had all the other defects together. We found it present in 21 per cent (seven of thirty-six cases) as compared with 23 per cent of the cases in the series studied by Boyd and McGavack. The next most common anomaly found at necropsy was interventricular septal defect, which was present in four cases. Present in one case each were aortic hypoplasia, bicuspid pulmonary valves, and double branch of the subclavian artery. Since these anomalies were detected only at necropsy, it is reasonable to suppose similar lesions to be present in those patients concerning whom the clinical diagnosis of aneurysm has been made.

Mycotic Degeneration of the Wall of the Pulmonary Artery: This was found in four cases of aneurysm. In these cases the lesion was associated with either infected patent ductus arteriosus or subacute bacterial endocarditis with valvular vegetation. A much larger group of patients who had mycotic aneurysm was excluded from our study because the involvement was, as seen more commonly, in the secondary and peripheral branches, where the infected embolus is more likely to implant. Omitted also was a group of more than seventy-five cases of small aneurysms associated primarily with tuberculous cavities.

Atheroma: Atheroma was mentioned as a significant observation in eleven necropsies. Such sclerosis appeared to be secondary to physiologic alterations of the pulmonary circuit. In three of these eleven instances there was marked arteriosclerosis throughout the lungs, with right cardiac dilatation. In the case which we shall report herein, only the right pulmonary artery was involved, yet all the arterioles in both lungs exhibited moderately severe sclerosis. In several cases patchy atheromatous deterioration of the pulmonary artery was associated with patent ductus arteriosus or septal defect.

Trauma: Trauma plays a very questionable role, even though it was listed as a probable etiology in three of the 139 cases of Boyd and McGavack.⁷ In the case which we shall report there was a history of minor trauma to the chest. At necropsy, however, pulmonary atheroma and arteriolosclerosis, as well as a large patent ductus arteriosus, was found. The presence of these lesions discounts the probable role trauma played.

On the basis of this analysis of the cases we have collected, it appears reasonable to state that in some instances it is difficult to be certain of the exact etiology, because a combination of the aforementioned conditions frequently is present. Of these, trauma seems to be the least common and least definite cause.

Diagnosis.—Clinical data were available in thirty-five of the series we collected from the literature, and although in some of them the reports were brief or fragmentary, it has been possible to enumerate the signs, symptoms, and physical observations most commonly encountered in the group (Table VI).

As in other series of cases, in the present series we found exertional dyspnea to be about the most common manifestation of aneurysm of the pulmonary

TABLE VI. SIGNS AND SYMPTOMS AS RECORDED IN THIRTY-FIVE CASES OF ANEURYSM OF THE PULMONARY ARTERY FROM THE LITERATURE

SYMPTOMS	PRESENT IN CASES, NUMBER	PER CENT	SIGNS	PRESENT IN CASES, NUMBER	PER CENT
Dyspnea	24	69	Murmur		
Cyanosis	20	57	Systolic	19	55
Edema	14	40	Diastolic	3	8
Cough	13	37	Thrill	8	23
Hemoptysis	11	31	Heart enlarged		
Pain	6	17	Right side	22	63
Clubbing	4	11	Entire heart	8	23
Ascites	4	11	Left side	1	3
Tachycardia	3	8	Electrocardiogram		
Epistaxis	2	6	Right axis deviation	12	(75)
Underdevelopment	2	6	Normal	3	
Scoliosis	1	3	Left bundle branch block	1	
Fainting	1	3	Polycythemia	6	17
Fatigue	1	3	Anemia	2	6
Pulmonary edema	1	3	Leucocytosis	2	6
			X-ray positive	20	57
			Anteroposterior projection,		
			orthodiagram, roentgenokymogram,		
			angiocardigram, teleroentgeno-		
			gram, tomogram, pneumomedias-		
			tinum		
			Test for syphilis		
			Positive	10	29
			Negative	7	20

artery. Frequently associated with this were cough, often with hemoptysis, and some form of thoracic pain. This latter symptom varied in character and extent, but most commonly the pain was precordial, with occasional extension to the shoulder and down the arm. In a few instances in which the aneurysm had enlarged suddenly or ruptured, there was severe, sharp pain. Also encountered were sensations of fullness, suffocation, pressure, or tightness in the chest. Cyanosis, although it was seen frequently, usually was a late development, occurring most often in the presence of congestive heart failure. Its early appearance usually was due to some congenital cardiac lesion which in itself causes cyanosis or to primary pulmonary arteriosclerosis.² Aneurysm infrequently causes clubbing of the fingers and toes, unlike pulmonary arteriovenous fistula.⁴⁰ Fever, anemia, and leucocytosis generally are seen only in the presence of bacterial endarteritis. Underdevelopment likewise is indicative generally of a patent ductus arteriosus. Edema and ascites are seen associated with failure of the right side of the heart. In no instance was hoarseness a symptom, in contrast to aortic aneurysm.

Among the most characteristic physical observations is the somewhat harsh systolic murmur heard in the second or third intercostal space at the left border of the sternum; this was audible in nineteen cases. In a few of these cases a separate diastolic murmur was present as well. A distinct thrill was noted in eight cases. In the fusiform type of aneurysm or that in which a sac has been obliterated by a thrombus, it might be expected that these findings would be absent.

Enlargement of the heart would appear to depend on secondary factors such as pulmonary hypertension or cardiac decompensation. In the thirty-one cases in which mention was made of such an observation, enlargement involved the right side of the heart in 70 per cent, the entire heart in 25 per cent, and the left side of the heart in 5 per cent. In those hearts examined, dilatation was predominant, indicating either that exertion of an effect on the size of the heart is late in the course of the disease or that the enlargement is due to complicating lesions. The fact that the right side of the heart is most commonly affected has been confirmed by the orthodiagram and by the electrocardiogram. Of sixteen cases in which the electrocardiogram was recorded, there was right axis deviation in twelve (75 per cent). Three tracings were normal. Right bundle branch block was noted in two cases and left bundle branch block in one case.

There were distinctly abnormal markings in the roentgenograms of many of the patients. They were described in some detail in twenty instances. Generally, the lesion was revealed as a discrete, rounded shadow at the hilum, which by oblique view could be outlined beneath the arch and anterior to the aortic outline. Involvement of the latter was excluded with care, since aortic aneurysm is not uncommon. The vascular nature of the lesion was confirmed in most instances by roentgenoscopy, as in the case we shall report. The peculiar expansile pulsation is transmitted through the lesser radicals of the pulmonary artery to result in what has been described as Pezzi's sign, or the characteristic "hilar dance."⁷⁴ It should be noted, however, that there have been instances of aneurysm of the pulmonary artery, confirmed by necropsy, in which no pulsation

had been seen at roentgenoscopy. An additional sign, the triangular cardiac shadow of Laubry and Bordet, has been described.⁷⁴ This distortion occurs when cardiac rotation results from the pulmonary dilatation, burying the apex in the diaphragm. These signs have been referred to primarily in French and Latin-American literature. Occasionally, other techniques have been employed to establish the diagnosis clinically. The roentgenokymogram was used in two cases to define the range of pulsation. The orthodiagram, teleroentgenogram, and tomogram also have been employed.

The diagnosis in four cases, which we have not included in our group of patients who had proved aneurysm, was made clinically on the basis of angiocardiology. In the case of Luisada and Sossai,⁶¹ pneumomediastinum was employed, in addition to arteriography with sodium iodide, to outline a saccular dilatation of the left pulmonary artery. In view of the syphilitic history of the patient, there is good presumptive evidence that this saccular dilatation was an aneurysm. Robb and Steinberg⁸⁸ in 1940, in a description of the patients studied by their technique of roentgenologic visualization of the heart and great vessels, mentioned two cases in which they had diagnosed the condition as aneurysm of the pulmonary artery. The lesions previously had been diagnosed as "aortic aneurysm" and "bronchiogenic carcinoma." Thompson⁹⁹ in 1941, conversely, employed an intravenous contrast medium to demonstrate pulmonary neoplasm and aortic aneurysm in two cases in which the condition had been diagnosed as "aneurysm of the pulmonary artery."

Stewart, Breimer, and Maier⁹⁶ in 1941 modified the method of Robb and Steinberg⁸⁴⁻⁸⁸ in that a motion picture was made of the passage of the contrast medium through, first, the pulmonary circuit, and then, the left side of the heart and aorta as viewed on the roentgenoscopic screen. Of four patients studied in this way, one a 22-year-old man, was found to have an interventricular septal defect as well as irregular dilatation of the pulmonary artery.

Although Carvalho and Moniz¹² (1931) pioneered in the use of pulmonary arteriography, it has been the recent improvements in angiocardiology that have increased the safety and accuracy of this method of cardiovascular diagnosis.^{29,67,72-84-87,94,97} Nevertheless, considerable uncertainty still exists in the clinical diagnosis of pulmonary aneurysm.

REPORT OF A CASE

This case is especially interesting because of the confusing history of the patient. The correct clinical diagnosis was confirmed by post-mortem examination.

A 37-year-old white man registered at the Mayo Clinic on Nov. 13, 1945, complaining of lymph nodes that had been enlarged since 1937. He brought with him a provisional diagnosis of lymphosarcoma of the Hodgkin type.

History.—The patient had diphtheria at the age of 8 years. He had four attacks of pneumonia, at the ages of 8, 13, 31, and 36 years. It had been said that he had leakage of the heart valves as a child. He had not had other diseases and had not undergone operation. In 1942, he had been struck in the right side of the chest with an airplane propeller blade. He had worked for a commercial airline company in Brazil from 1943 to 1945.

Condition Prior to the Time of Registration.—In 1937 an insidious cough, with some degree of hemoptysis, had developed. At the appearance of low, intermittent fever and generalized lymphadenopathy, he had been hospitalized for eleven weeks. Roentgen-ray treatments had been administered, with some symptomatic relief. Since February, 1945, the patient had experienced bimonthly and trimonthly episodes of fever in which his temperature was as high as 101° F. (38.3° C.), accompanied by some degree of nausea, abdominal discomfort, and diarrhea. The liver of the patient was somewhat enlarged. Roentgenograms of his thorax had then revealed what were believed to be enlarged mediastinal lymph nodes. The patient again had received a series of deep irradiation treatments. In September, 1945, he had become increasingly weak. He had been subject to fleeting pains in the right side of the thorax, occasional epistaxis, and dyspnea. When lying on his left side he had noted a "strangling" sensation. If he became cold, he exhibited slight cyanosis. Otherwise, he complained of nothing significant.

Physical Examination.—The blood pressure at systole was 110/74. Oral temperature was normal. At the time of the initial examination the patient did not have cyanosis, but did have it on subsequent occasions. Clubbing of the great toes was noted. Tenderness was present over the anterior wall of the thorax on the right, particularly near the sternum. There was definite lymphadenopathy of the cervical, axillary, and inguinal lymph nodes. Repeated examination of the heart revealed no murmurs, thrills, or enlargement.

Laboratory Examinations.—The urine was entirely normal. Results of Kahn and Kline tests of the serum were negative. The value for hemoglobin was 16.0 grams per 100 c.c. of blood. Erythrocytes numbered 5,300,000 per cubic millimeter. Leucocytes amounted to 9,500 per cubic millimeter. The differential leucocyte count disclosed that 11 per cent were lymphocytes, 10 per cent were monocytes, 72 per cent were polymorphonuclear leucocytes, and 7 per cent were eosinophils. Results of study of the sputum were negative for the organisms of tuberculosis and for pathogenic fungi. Results of Mantoux tests, in which purified protein derivative was used in two strengths, were negative in forty-eight hours. The test for hepatic function revealed no retention of dye. The sedimentation rate (Westergren) was 7 mm. in one hour. Result of the direct test for serum bilirubin was negative; result of the indirect test was 0.7 mg. per 100 cubic centimeters. An electrocardiogram made with three standard leads showed a rate of 58, sinus arrhythmia, slurred QRS complex in Leads I and III, right axis deviation, low T wave in Lead I, and inverted T wave in Leads II and III.

Roentgenologic Examination.—On Nov. 14, 1945, stereoscopic anteroposterior roentgenograms revealed a well-defined mass in the right perihilar region. On Nov. 14 and 16, 1945, roentgenograms made with a Bucky diaphragm and in the anteroposterior and lateral projections showed this mass to contain calcium in the walls (Fig. 1, *a* and *b*). The presence of a Ghon complex with fibrosis in the left third intercostal space anteriorly raised the question of tuberculoma, although dermoid tumor also was considered. On Nov. 19, 1945, by means of roentgenoscopic examination, a slight but definite expansile pulsation of the mass in the right hilum was noted, and the diagnosis of aneurysm of the right pulmonary artery was made.

To exclude the possibility that other hilar lesions may have contributed to the patient's symptom complex, bronchoscopy was carried out on Nov. 21, 1945. No evidence of tumor was demonstrated thereby. The medial wall of the right main bronchus at the level of the hyparterial bronchi of the right lung pulsated much more than is seen normally. The question of the presence of an arteriovenous aneurysm of the lung was raised. Consequently, additional studies were made.

On Nov. 23, 1945, a tomogram of the right hilar region delineated an aneurysmal sac, with calcification of the walls (Fig. 2, *a*). No outpocketings were observed. Oxygen saturation studies were performed: the arterial blood was found to be 91 per cent saturated; venous blood was shown to be 47.6 per cent saturated; the oxygen capacity was 23.5 volumes per cent.

Treatment.—It was hoped that ligation of the right pulmonary artery could be performed close to the trunk, so that the aneurysm, which appeared to be the size of a small orange in roentgenograms, might thus be removed. In this event, pneumonectomy naturally would follow.



Fig. 1.—*a*, Anteroposterior roentgenogram made on Nov. 14, 1945, one day after admission of the patient, demonstrating aneurysm of the pulmonary artery in the right hilar region; *b*, lateral view, made on Nov. 16, 1945.



Fig. 2.—*a*, Tomogram made on Nov. 23, 1945, showing the patchy calcification of the wall of the aneurysm; *b*, postoperative view, made on Nov. 30, 1945, showing enlargement of both the cardiac shadow and that of the aneurysm.

The situation was discussed with the patient. He decided to allow an attempt to remove the aneurysm surgically.

On Nov. 29, 1945, after three days of preparation of the patient in the hospital with rest and intramuscular injection of 120,000 units of penicillin daily, exploratory thoracotomy was performed with the patient anesthetized with ether-oxygen administered by the closed system. The aneurysm was found to involve the right pulmonary artery and to extend into the pericardial space, as well as to that branch of the pulmonary artery supplying the lower lobe of the right lung. The extremely atheromatous calcification of the walls of the artery precluded further surgical manipulation. After 500 c.c. of whole citrated blood had been transfused, the patient was returned to his room in good condition. He was placed in an oxygen tent and was restricted in the intake of water by mouth postanesthetically. Penicillin was administered in the same dosage



Fig. 3.—Heart and right lung. The aneurysm has been cut open to reveal the split in the atheromatous wall.

that had been used preoperatively. On Nov. 30, 1945, coarse râles and rhonchi and a high degree of cyanosis developed, even though the patient had been kept in the oxygen tent. A roentgenogram of the thorax made with a portable machine showed congestion and slight enlargement of the aneurysm (Fig. 2, b). In the hope of clearing the patient's airways, bronchoscopy was carried out on Nov. 30, 1945. There was almost no secretion to be aspirated, but marked gastric retention had occurred. The patient's pronounced cyanosis could be only partly relieved by the inhalation of 100 per cent oxygen. His condition remained about the same until early on Dec. 2, 1945, when a sudden increase in pulse rate and respiratory difficulty developed. A cardiac stimulant (cedilanid) was administered, but the patient rapidly died from respiratory failure.



Fig. 4.—Heart and great vessels: *a*, marked hypertrophy of the wall of the right ventricle and the atheromatous plaques of the pulmonary arterial wall; a probe marks the mouth of the patent ductus arteriosus; *b*, the opening of the ductus arteriosus into the aorta is clearly visible.

Pathologic Examination.—Pathologic examination was performed on Dec. 2, 1945. The body was somewhat emaciated, with clubbing of the great toes and cyanosis of the lips and nail beds. The thorax contained 200 c.c. of a serosanguineous effusion in the right pleural space as a result of the recent surgical intervention. The pericardial cavity contained 7 c.c. of yellow fluid. The thymus gland was atrophic. In the heart, marked hypertrophy of the right auricle and ventricle was noted, the left side being normal. The foramen ovale was closed. A saccular aneurysm of the right pulmonary artery, 3 by 7 cm., was found (Fig. 3). The walls of the vessel were affected by a marked degree of sclerosis with calcification. An incomplete longitudinal split, 2.5 by 0.5 cm., involved the tunica intima. The left pulmonary artery was normal. The aorta exhibited slight sclerosis. There was a patent ductus arteriosus, 1 cm. in diameter (Fig. 4, *a* and *b*). There was mild sclerosis of the coronary arteries. The pulmonic valve measured 7.0 centimeters. There was an anomalous double branch of the left subclavian artery. The right lung was affected by atelectasis of the lower lobe. A few minimal tuberculous lesions were seen in the upper lobe of the left lung. The spleen weighed 123 grams. The liver weighed 1,543 grams. The gastrointestinal tract was normal, as was the pancreas, which weighed 80 grams. Each kidney weighed about 135 grams; each was normal. The bladder contained slightly bloody urine.

Microscopically, the right lung exhibited some evidence of bronchopneumonia and hemorrhagic edema. The upper lobe of the left lung had been affected by old fibrocaceous tuberculosis. Throughout both lungs, rather marked arteriolosclerosis was present, with many of the small vessels completely occluded or hyalinized.

COMMENT

The cause of this patient's lymphadenopathy and fever remains unknown. Careful analysis of the history demonstrates the difficulty in definitely determining the cause and duration of the aneurysm. We cannot say for certain what importance the patient's repeated bouts of pneumonia, the "valvular" disturbance reported to have been present when he was a child (patent ductus arteriosus?), the injury to his chest, or the pulmonary arteriosclerosis played in the etiology. Although the aneurysm may have developed in the patient's childhood, or in 1937 when cough and hemoptysis developed, it is also possible that the actual saccular enlargement did not occur until September, 1945. The late symptoms of pain in the right side of the thorax, dyspnea, and cyanosis would support such a view. Except for the electrocardiographic finding of right axis deviation, the significant laboratory observations were essentially those of the roentgenologic examinations. The description of a discrete rounded shadow in the perihilar region, distinct from the aortic silhouette, with calcified wall and a definite pulsatile character, agrees admirably with the usual description of aneurysm of the pulmonary artery.

Some nonpulsatile calcified tumors of this region which may be confused with aneurysm of the pulmonary artery are tuberculoma, abscess associated with Pott's disease, the hilar lymph nodes in the presence of tuberculosis or histoplasmosis, dermoid tumors, and substernal goiter. When both pulsation and calcification are absent, the diagnostician must keep in mind the possibilities of primary carcinoma of the lung, adenoma, mediastinal abscess or lymphadenopathy, lymphosarcoma, thymoma, and cysts of the mediastinum, lung, or pericardium, but it must also be remembered that pulmonary aneurysm has occurred unaccompanied by either pulsation or calcification.

The cause of death in the presence of aneurysm of the pulmonary artery is, most commonly, heart failure or rupture of the aneurysm. In this series of thirty-six cases, only four deaths were caused by rupture; two aneurysms ruptured into the pericardial space and two ruptured into a bronchus.

Since aneurysm of the thoracic aorta may most easily be confused with aneurysm of the pulmonary artery because of the general similarity of situation and frequent presence of calcification and pulsation associated with both conditions, we wish to point out some significant differences between the two. It has been determined, on the basis of a series of 160,000 necropsies, that the incidence of thoracic aortic aneurysm as encountered at necropsy will range from 1:200 in Germany to 1:40 in some parts of the United States.²³ At the Mayo Clinic, the ratio has been about 1:140 as compared to a ratio for pulmonary aneurysm of 1:17,545.⁵⁵ Groedel³⁰ has estimated that one pulmonary aneurysm occurs to 250 aneurysms of the aorta. We have seen that the average age of the patient is greater in the presence of aortic aneurysm than in aneurysm of the pulmonary artery, since about 85 per cent of patients who have aortic aneurysm are older than thirty years. The incidence according to sex also differs.^{6,23} In the case of the thoracic aorta, aneurysms have occurred in the white race in the ratio of four males to one female, whereas in the Negro, this ratio is increased to

8:1. It is common knowledge that more Negroes than white people have such aortic aneurysms. The known increased incidence of syphilis among Negroes may account for the greater incidence of aortic aneurysms among them. When pulmonary aneurysm is considered, on the other hand, it is found that the incidence of aneurysm of the pulmonary artery according to sex is equal. There were only two Negroes in the thirty-six cases we have collected. Syphilis has been said to cause up to 95 per cent of aneurysms of the thoracic aorta, whereas syphilis was definitely proved to exist in only about a third of the aneurysms of the pulmonary artery. These significant differences would suggest that some difference in physiologic mechanisms of production was active in the two lesions.

SUMMARY

An analysis has been presented of a series of thirty-six cases of aneurysm of the pulmonary artery, proved by necropsy and collected from the literature. The addition of this group to the 111 cases proved at necropsy and reported by Boyd and McGavack⁷ in 1939 brings the total number of authentic cases to 147. The advisability of omitting cases in which only the clinical diagnosis has been made is pointed out. The facts that the incidence according to sex is the same and that the patients concerned are relatively younger help to distinguish this type of aneurysm from that of the thoracic aorta. Although syphilis was a definite factor in more than a third of the cases, congenital cardiovascular anomalies also play a major role. A patent ductus arteriosus is present in more than 20 per cent of cases. Other less common causes are subacute bacterial endarteritis, atheroma, and trauma.

The early symptoms are dyspnea, cough, and pain in the thorax. Cyanosis and edema usually are later manifestations, often dependent on cardiac failure or congenital anomalies. The heart, especially the right ventricle, frequently is enlarged. Right axis deviation is common in the electrocardiogram. Most significant is the roentgenologic and roentgenoscopic finding of a discrete pulsatile hilar mass, separate from the aortic shadow. Usually, no special means of examination is necessary as a supplement to roentgenoscopy, although tomography, arteriography, roentgenokymography, and pneumomediastinum have been employed.

A detailed report of a case is presented. The condition of the patient was interesting in that the clinical diagnosis was confirmed by necropsy. There were a patent ductus arteriosus, atheroma of the right pulmonary artery, and bilateral pulmonary arteriolosclerosis, as well as a history of trauma. Surgical cure by ligation of the right pulmonary artery and pneumonectomy was prevented by the extent of the aneurysm and the atheromatous calcification of the vessel concerned.

REFERENCES

1. Allan, W. B., and McCracken, J. P.: Aneurysm of the Pulmonary Arteries, *Am. J. Syph., Gonorr. & Ven. Dis.* 24:563, 1940.
2. Arrillaga, F. C.: Sclérose de l'artère pulmonaire secondaire a certains états pulmonaires chroniques (cardiaques noirs), *Arch. d. mal. du coeur.* 6:518, 1913.

3. Arrillaga, F. C.: Sclérose de l'artère pulmonaire (cardiaques noirs), Bull. et mém. Soc. méd. d. hôp. de Paris 1:292, 1924.
4. Auerbach, Oscar: Pathology and Pathogenesis of Pulmonary Arterial Aneurysm in Tuberculous Cavities, Am. Rev. Tuberc. 39:99, 1939.
5. Bello, Domenico: Arterite luetica "isolata" ed aneurisma del tronco della polmonare in corso di stenosi mitralica. Contributo ai rapporti tra ipertensione distrettuale e localizzazione arteritica luetica, Arch. "de Vecchi" per anat. pat. e med. clin. 1:508, 1939.
6. Boyd, L. J.: A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta, Am. J. M. Sc. 168:654, 1924.
7. Boyd, L. J., and McGavack, T. H.: Aneurysm of the Pulmonary Artery; a Review of the Literature and Report of Two Cases, AM. HEART J. 18:562, 1939.
8. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation. Part II; Part V, Arch. Int. Med. 56:457, 1189, 1935.
9. Breslin, L. J., Solway, L. J., and Eisen, D.: Aneurysms of Pulmonary Artery (With Case Report), Canad. M. A. J. 45:61, 1941.
10. Bristowe, L. S.: Thickening and Dilatation of the Pulmonary Artery, and Its Ramifications, Tr. Path. Soc. London 11:80, 1860.
11. Cañedo, Ruben: Dilatacion aneurismatica de la arteria pulmonar, Rev. san. mil., Habana 7:121, 1943.
12. Carvalho and Moniz: Quoted by Robb and Steinberg.⁸⁵
13. Clausen, Arne: Peripheres Aneurysma in der art. pulmonalis, Acta radiol. 26:324, 1945.
14. Clerc, A., and Frain, C.: Dilatation du tronc de l'artère pulmonaire, Arch. d. mal. du coeur. 37:57, 1944.
15. Cossio, P., and Arana, R. S.: Communication inter-auriculaire, Bull. Acad. de méd., Paris 117:212, 1937.
16. Costa, A.: Morfologia e patogenesi degli aneurismi dell'arteria pulmonare. (Sopra in caso di voluminosi aneurismi multipli del tronco e dei grossi e medi rami. su base malformativa.) Arch. di pat. e clin. med. 8:257, 1929; (Abst.) Morphologie und Pathogenese der Aneurysmen der Arteria pulmonalis, Zentralbl. f. allg. Path. u. path. Anat. 52:8, 1931.
17. Crisp, E.: Quoted by Scott.⁹¹
18. Cruzon O., and Grenaudier: Un cas de dilatation de l'artère pulmonaire a son origine, Bull. et mém. Soc. méd. d. hôp. de Paris 1:34, 1922.
19. D'Aunoy, Rigney, and von Haam, Emmerich: Aneurysm of the Pulmonary Artery With Patent Ductus Arteriosus (Botallo's Duct); Report of Two Cases and Review of the Literature, J. Path. & Bact. 38:39, 1934.
20. Deschamps, P. N.: Un cas d'anévrysme de l'artère pulmonaire? Arch. d. mal. du coeur 37:52, 1944.
21. Dlahý: Quoted by D'Aunoy and von Haam.¹⁹
22. Duperie, R., and de Lachaud, R.: Un cas d'anévrysme de l'artère pulmonaire rompu dans le péricarde, J. de méd. de Bordeaux 116:526, 1939.
23. Geraci, A. S.: Syphilitic Aneurysm of the Thoracic Aorta, Urol. & Cutan. Rev. 44:508, 1940.
24. Gibson, Stanley: The Clinical Significance of Heart Murmurs in Children, M. Clin. North America 30:35, 1946.
25. Giroux: Sclérose et athérome de l'artère pulmonaire. Role des conditions mécaniques, Arch. d. mal. du coeur 3:218, 1910.
26. Gonzalez-Sabathie, L.: Los aneurismas de la arteria pulmonar, Día méd. 6:378, 1933.
27. Gonzalez-Sabathie, L.: Aneurisma de la rama izquierda de la arteria pulmonar, Rev. argent. de cardiología. 2:117, 1935.
28. Gonzalez-Sabathie, L.: Aneurysma des linken Astes der Arteria pulmonalis, (Abst.) Ztschr. f. Kreislaufforsch. 28:461, 1936.
29. Grishman, A., Steinberg, M. F., and Sussman, M. L.: Tetralogy of Fallot: Contrast Visualization of Heart and Great Vessels, Radiology 37:178, 1941.
30. Groedel, F. M.: Aneurysm of the Pulmonary Artery, Radiology 33:219, 1939.
31. Hamilton, W. F., and Abbott, Maude E.: Patent Ductus Arteriosus With Acute Infective Pulmonary Endarteritis, Tr. A. Am. Physicians 29:294, 1914.
32. Hartwell, A. S., and Tilden, I. L.: Aneurysm of the Pulmonary Artery; Report of a Case in Which the Aneurysm Apparently Developed Under Observation, AM. HEART J. 26:692, 1943.
33. Hasegawa, Fukashi, and Kumabe, Hideo: Ueber das Rassmussensche Aneurysma, Tr. Soc. path. jap. 29:72, 1939.
34. Hebb, R. G.: Aneurysm of Ductus Arteriosus and Atheroma of Pulmonary Artery, Tr. Path. Soc. London 44:45, 1893.
35. Henschen, C.: Maladies de l'artère pulmonaire et interventions chirurgicales, Presse méd. 2:520, 1945.
36. Henschen, S. E.: Quoted by Boyd.⁴

37. Höra, I., and Wendt, H.: Thromboendarteriitis der Lungenschlagader mit multiplen, mykotischen Aneurysmen, *Wien. Arch. f. inn. Med.* 35:249, 1941.
38. Jennes, S. W.: Diffuse Aneurysmal Dilatation of the Pulmonary Artery and Both of Its Branches, *Bull. Johns Hopkins Hosp.* 59:133, 1936.
39. Johansen, M. W., and Connor, C. A. R.: Cor Pulmonale With Bilateral Aneurysms of the Pulmonary Artery, Interventricular-Septal Defect, Patent Ductus Arteriosus and Terminal Ayerza's Syndrome, *Ann. Int. Med.* 18:232, 1943.
40. Jones, J. C., and Thompson, W. P.: Arteriovenous Fistula of Lung; Report of Patient Cured by Pneumonectomy, *J. Thoracic Surg.* 13:357, 1944.
41. Jouve, A., Delaage, M., and Oddo, R.: Dilatation congénitale de l'artère pulmonaire; tuberculose cavitare, hémoptysie foudroyante, *Arch. d. mal. du coeur.* 37:52, 1944.
42. Käppeli, A.: Ueber einen Fall von Aneurysma der Pulmonalarterie, *Ztschr. f. klin. Med.* 123:603, 1933.
43. Karsner, H. T.: Productive-cicatricial Syphilitic Disease of the Pulmonary Artery, *Arch. Int. Med.* 51:367, 1933.
44. Kates, S. R.: Aneurysm of the Pulmonary Artery Perforating Into the Pleural Cavity, With Recovery, *M. Bull. Vet. Admin.* 17:390, 1941.
45. Kidd, Percy: Unusual Cases of Pulmonary Aneurysm, *Tr. Path. Soc. London* 35:98, 1884.
46. Kidd, Percy: Embolic Aneurysm of the Pulmonary Artery; Infective Aortic Valvulitis, Aortitis, and Endarteritis; Patent Ductus Arteriosus, (Card specimen.) *Tr. Path. Soc. London* 44:47, 1893.
47. Klotz, M.: Quoted by Scott.⁹¹
48. Krzyszkowski, Josef: Aneurysma des Stammes der Pulmonalarterie und multiple Aneurysmen ihrer Verästelungen bei Persistenz des Ductus Botalli, *Wien, klin. Wchnschr.* 15:92, 1902.
49. Laubry, C.: A propos des dilatations congénitales de l'artère pulmonaire, *Arch. d. mal. du coeur.* 36:61, 1943.
50. Laubry, C., and Parvu, M.: Lésion complexe de l'artère pulmonaire d'origine congénitale, *Bull. et mém. Soc. méd. d. hôp. de Paris* 2:1395, 1920.
51. Laubry, C., and Routier, Daniel: La dilatation congénitale de l'artère pulmonaire, *Bull. Acad. de méd., Paris* 124:126, 1941.
52. Laubry, Charles, and Thomas, Marcel: Les formes anatomo-cliniques des artérites pulmonaires chez les syphilitiques, *Bull. et mém. Soc. méd. d. hôp. de Paris* 1:9, 1927.
53. Laubry, C., Routier, D., and Heim De Balsac, R.: Grosse pulmonaire. Petite aorte. Affection congénitale, *Bull. et mém. Soc. méd. d. hôp. de Paris* 56:847, 1941.
54. Lelli, G.: Multiple mykofische Aneurysmen der Lungenarterien bei ulzeröser Endokarditis der Aortenklappen und offenem Ductus Botalli, *Zentralbl. f. allg. Path. u. path. Anat.* 77:342, 1941.
55. Lenègre, J., Roudinesco, J., and Marquis, G.: Deux cas de dilatation segmentaire congénitale de l'artère pulmonaire, *Arch. d. mal. du coeur.* 36:55, 1943.
56. Lenègre, J., Roudinesco, J., and Marquis, G.: Dilatation segmentaire congénitale de l'artère pulmonaire (résultats de l'autopsie), *Arch. d. mal. du coeur* 37:12, 1944.
57. Lequime, J., van Heerswynghe, J., and Herlant, M.: Contribution à l'étude de la dilatation congénitale de l'artère pulmonaire, *Arch. d. mal. du coeur* 37:7, 1944.
58. Long, M.: Unpublished data.
59. Lucke and Rea: Quoted by Scott.⁹¹
60. Luisada, A.: Aneurisma vero dell'arteria pulmonare da arterite luetica, *Minerva med.* 2:421, 1934.
61. Luisada, A., and Sossai, A.: La méthode de Schuntermann pour la mesure de la tension dans l'artère pulmonaire contrôlée directement dans un cas d'anévrysme de la même artère, *Arch. d. mal. du coeur* 32:175, 1939.
62. McGinn, Sylvester, and White, P. D.: Interauricular Septal Defect Associated With Mitral Stenosis, *AM. HEART J.* 9:1, 1933.
63. Mills, J. H., and Horton, B. T.: Clinical Aspects of Aneurysm, *Arch. Int. Med.* 62:946, 1938.
64. De Navasquez, S.: Aneurysm of the Pulmonary Artery and Fibrosis of the Lungs Due to Syphilis, *J. Path. & Bact.* 54:315, 1942.
65. Nikolaiew: Diagnostic de l'anévrysme de l'artère pulmonaire, *Arch. d. mal. du coeur* 11:128, 1918.
66. Nixon, J. W.: Surgical Ligation of Patent Ductus Arteriosus Associated With Aneurysm of Pulmonary Artery; Report of Successful Case, *J. Thoracic Surg.* 13:513, 1944.
67. Olney, Mary B., and Miller, E. R.: Use of Intravenous Cardiography in the Study of Congenital Heart Disease With Cyanosis, *Clinics* 3:235, 1944.
68. Oppenheimer, B. S.: Idiopathic Dilatation of the Pulmonary Artery, *Tr. A. Am. Physicians* 48:290, 1933.

69. Palmer, H. D., and Kempf, Myrna: Streptococcus Viridans Bacteremia Following Extraction of Teeth; a Case of Multiple Mycotic Aneurysms in the Pulmonary Arteries: Report of Cases and Necropsies, J. A. M. A. 113:1788, 1939.
70. Patel, N. D.: Pulmonary Hypertension; Report of a Case of Interauricular Septal Defect, Aneurysmal Dilatation of Pulmonary Artery, and Eosinophilia, Indian Physician 3:9, 1944.
71. Peck, S. M.: Pathologic Anatomy of Syphilis of the Pulmonary Artery; Report of a Case and Review of the Literature. Arch. Path. 4:365, 1927.
72. Pérez de los Reyes, Rodolfo, Castellanos, Agustin, and Pereiras, Raul: Angiocardiography and Its Value, AM. HEART J. 25:298, 1943.
73. Pérez Simón, Armando: Aneurisma de la arteria pulmonar. Un caso clinico, Vida nueva 52:90, 1943.
74. Pezzi, C., and Silingardi, S.: A propos d'un cas d'ectasie de l'artère pulmonaire avec insuffisance de l'appareil valvulaire; signe radioscopique d'insuffisance pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris 1:117, 1925.
75. Pissot, Pauline M.: Contribution à l'étude de l'anévrysme de l'artère pulmonaire, Thesis, Paris, 1920, 50 pp.
76. Plencznev, Alexander: Seltener Fall eines Aneurysmas der Art. Pulmonalis, Ztschr. f. Kreislaufforsch. 31:881, 1939.
77. Plenge, Karl: Zur Frage der Syphilis der Lungenschlagader, Virchows Arch. f. path. Anat. 275:572, 1930.
78. Posselt, A.: Die Erkrankungen der Lungenschlagader, Ergebn. d. allg. Path. u. path. Anat. 13:298, 1909.
79. Queyrat, Gandy, and Deguignand: Cardiopathie congénitale (rétrécissement mitral et dilatation de l'artère pulmonaire) vraisemblablement d'origine hérédo-syphilitique, Bull. et mém. Soc. méd. d. hôp. de Paris 1:608, 1921.
80. Raynaud, R., Tillier, H., and Huguenin, A.: Un cas d'anévrysme de l'artère pulmonaire, Bull. et mém. Soc. d'électro-radiol. méd. de France 26:656, 1938.
81. Reeke, T.: Ueber Syphilis der Pulmonalarterie, Zentralbl. f. allg. Path. u. path. Anat. 49:257, 1930.
82. Reiner, O.: Erweiterung der Lungenschlagader und Insuffizienz der Pulmonalklappen, Deutsche med. Wchnschr. 66:1272, 1940.
83. Ribierre, P., and Giroux, René: Sclérose de l'artère pulmonaire secondaire a des processus broncho-pulmonaires, Bull. et mém. Soc. méd. d. hôp. de Paris 2:1465, 1921.
84. Robb, G. P., and Steinberg, Israel: A Practical Method of Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man, J. Clin. Investigation 17:507, 1938.
85. Robb, G. P., and Steinberg, Israel: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man; A Practical Method, Am. J. Roentgenol. 41:1, 1939.
86. Robb, G. P., and Steinberg, Israel: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Heart Disease; Preliminary Observations, Am. J. Roentgenol. 42:14, 1939.
87. Robb, G. P., and Steinberg, Israel: Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease; a Case Study, Ann. Int. Med. 13:12, 1939.
88. Robb, G. P., and Steinberg, Israel: Visualization of the Chambers of the Heart; the Pulmonary Circulation and the Great Blood Vessels in Man: Summary of Method and Results, J. A. M. A. 114:474, 1940.
89. Routier, D., and Heim de Balsac, R.: Remarques sur les modifications dans le temps des "grosses artères pulmonaires," Arch. d. mal du coeur 36:58, 1943.
90. Rundles, R. W.: Hemorrhagic Telangiectasia With Pulmonary Artery Aneurysm: Case Report, Am. J. M. Sc. 210:76, 1945.
91. Scott, R. B.: Aneurysm of the Pulmonary Artery; With Report of a Case, Lancet 1:567, 1934.
92. Sisson, J. H., Murphy, G. E., and Newman, E. V.: Multiple Congenital Arteriovenous Aneurysms in the Pulmonary Circulation, Bull. Johns Hopkins Hosp. 76:93, 1945.
93. Soulie, P., Bouvrain, Y., and Joly, F.: Les formes partielles de la dilatation congénitale de l'artère pulmonaire, Arch. d. mal. du coeur 36:49, 1943.
94. Steinberg, Israel, Robb, G. P., and Roche, Ursula J.: The Differential Diagnosis of Mediastinal Tumor and Aortic Aneurysm; Value of Contrast Cardiovascular Visualization, New York State J. Med. 40:1168, 1940.
95. Steinberg, William: Zur Kenntnis des mykotischen Aneurysmas der Lungenschlagader, Virchows Arch. f. path. Anat. 290:433, 1933.
96. Stewart, W. N., Breimer, C. W., and Maier, H. C.: Cineroentgenographic Diagnosis of Congenital and Acquired Heart Disease, Am. J. Roentgenol. 46:636, 1941.
97. Sussman, M. L., Grishman, Arthur, and Steinberg, M. F.: Newer Concepts in the Diagnosis of Congenital Heart Disease, Am. J. Dis. Child. 65:922, 1943.

98. Thomas, Marcel: Contribution à l'étude des affections acquises de l'artère pulmonaire, Thesis, Alcan, 1927, 172 pp.
99. Thompson, S. A.: Differential Diagnosis by Means of Intravenous Contrast Medium of Two Cases Simulating Aneurysm of the Pulmonary Artery, *Am. J. Roentgenol.* 46: 646, 1941.
100. Waite, W. W.: Aneurysm of the Pulmonary Artery, *Texas State J. Med.* 34:535, 1938.
101. Warthin, A. S.: Syphilis of the Pulmonary Artery: Syphilitic Aneurysm of Left Upper Division: Demonstration of Spirochete Pallida in Wall of Artery and Aneurysmal Sac, *Am. J. Syph.* 1:693, 1917.
102. Warthin, A. S.: The New Pathology of Syphilis, *Am. J. Syph. & Ven. Dis.* 2:425, 1918
103. West, Samuel: Case of Aneurysm of a Branch of the Pulmonary Artery; Death From Haemorrhage, *Tr. Soc. Path., London* 29:41, 1877-1878.
104. West, Samuel: Two cases of Complete Excavation of One Lung, With Death in One Case From Exhaustion; in the Other From Rupture of an Aneurysm of the Pulmonary Artery, *Tr. Path. Soc., London* 31:50, 1880.
105. West, Samuel: Aneurysm of the Pulmonary Artery, *Tr. Path. Soc., London* 32:67, 1881.
106. West, Samuel: Two Cases of Pulmonary Aneurysm of Large Size, With Profuse Recurrent Haemoptysis for Twelve and Forty-five Days Respectively, With Remarks Upon Pulmonary Aneurysms in General, *Tr. Path. Soc., London* 35:93, 1884.
107. Wildhagen: Aneurysma des Hauptstammes der Arteria pulmonalis, *Med. Klin.* 2:168, 1920.
108. Wilkinson, K. D.: Aneurysmal Dilatation of the Pulmonary Artery, *Brit. Heart J.* 2:255, 1940.
109. Wilks: Enlargement of the Pulmonary Artery in Contraction of the Mitral Orifice, *Tr. Path. Soc., London* 12:70, 1860.
110. Winternitz and Schmeisser: Quoted by Warthin.¹⁰¹
111. Wolff-Bremen, K.: Ueber eine in beiden Nieren gleichmässig verteilte herdförmige Xanthelasmatoze bei gleichzeitigen multiplen Aneurysmen der Lungenschlagader, *Ztschr. f. Krieslaufforsch.* 28:741, 1936.
112. Yuskis, A. S.: Aneurysm of the Right Pulmonary Artery; With Rupture Into Bronchus; and a Patent Ductus Arteriosus. Report of Case, *California & West. Med.* 58:272, 1943.

BLOCKED (NONCONDUCTED) A-V NODAL PREMATURE SYSTOLES IMITATING FIRST AND SECOND DEGREE A-V BLOCK

R. LANGENDORF, M.D., AND J. S. MEHLMAN, M.D.
CHICAGO, ILL.

BLOCKED, or more accurately, nonconducted premature systoles of auricular origin are of common occurrence. It is to be expected that premature impulses originating in the A-V node early in diastole may also find the conducting tissues between the site of origin of the ectopic impulse and the ventricles in a refractory state and, therefore, may not be conducted. Since the A-V nodal impulse normally may be conducted in two directions, backward to the auricles and forward to the ventricles, block of a nodal impulse may lead to the failure of (a) an auricular response (Fig. 4,A), (b) a ventricular response (Fig. 4,B), or (c) both an auricular and ventricular response (Fig. 4,C). Furthermore, such blocked or nonconducted premature A-V nodal impulses can be expected to exert an effect on the conduction of the subsequent sinus impulse, since the premature impulse would be propagated within the conducting tissues before being blocked or interfering with the sinus impulse. It will be shown that the effect of such concealed conduction within the A-V junction upon the subsequent sinus impulse may represent the only evidence of a blocked A-V nodal premature systole (Fig. 4,C and 4,D).

The following two cases are presented to illustrate the peculiar disturbances of cardiac rhythm caused by nonconducted A-V nodal premature systoles.

CASE 1.—The record illustrated in Fig. 1 was obtained on a 19-year-old white soldier in excellent health, on whom an electrocardiogram was taken to determine the mechanism of his pulse irregularity. A slight sinus arrhythmia is present, the distance between two upright P waves varying less than 0.08 second. It can be seen that whenever a lengthening of the R-R interval occurs, a premature P wave precedes the ventricular pause. These premature P waves (marked P₁ to P₆) are all inverted; they seem to differ in contour because they are superimposed on different portions of the S-T-T complex of the preceding sinus beat. P₂, P₄, and P₆ occurring late in diastole are followed by a ventricular complex identical with that of the sinus beats; P₁ and P₅, occurring much earlier, are not followed by a ventricular response. P₃, although occurring even earlier than P₁ and P₅, is followed by a ventricular complex with aberrant conduction.

From the Cardiovascular Department, Michael Reese Hospital.
Aided by the Herbert G. Mayer Fund for Cardiovascular Research.
The department is supported in part by the Michael Reese Research Foundation.
Received for publication Nov. 21, 1946.

The P-R intervals of the premature impulses of P_2 , P_4 , and P_6 measure 0.12 second as compared to the P-R of 0.17 second of the sinus beats. This fact and the retrograde contour of the P wave (Leads I and III which are not reproduced show small upright and deeply inverted premature P waves, respectively) justify a diagnosis of A-V nodal rather than auricular premature systoles; the premature systoles are most likely all from the same focus. For that reason, P_1 and P_5 represent premature systoles of A-V nodal origin conducted in a retrograde fashion to the auricles but not conducted to the ventricles. The impulse of P_3 shows a prolonged P-R interval (0.22 second) as a result of delayed forward conduction and a prolonged QRS (0.13 second) as a result of incomplete recovery of the fibers responsible for intraventricular conduction.

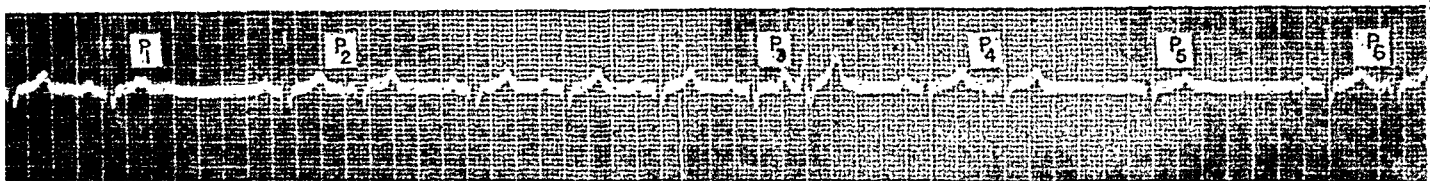


Fig. 1.—Blocked A-V nodal premature systoles imitating blocked auricular premature systoles. Discussed in text.

The great variations in the coupling of the premature P waves to the preceding sinus beats with only slight variations of the P-P intervals of the extrasystolic beats suggest a parasytolic pacemaker. Exactly even spacing of the extrasystolic P waves cannot be expected since the length of the extrasystolic P-P intervals is expected to vary with variations of the retrograde conduction time.

The impulse of P_3 is conducted to the ventricles, although it occurs apparently earlier in diastole than the nonconducted impulse of P_1 and P_5 . Unfortunately the available material was insufficient to allow a conclusion as to whether the phenomenon was indicative of a supernormal phase of conduction or of varying retrograde conduction.

CASE 2.—The records presented in Figs. 2 and 3 were taken on a 44-year-old white man who had experienced several attacks of aching retrosternal pain, occurring with strenuous exertion, in the past two and one-half years. A cardiac irregularity had been discovered at about the time of the first such episode. About six months before these records were taken, the patient suffered a sudden loss of consciousness for about two minutes, attributed to bending over and lifting a heavy object. The only other complaint was of palpitation, not related to pain. There were no abnormal physical findings except for the cardiac arrhythmia. The circulation time and vital capacity were within normal limits. Carotid sinus stimulation, quinidine sulfate, and atropine medication were all ineffective in altering the rhythm. An electrocardiogram after a Master "two-step" test showed no changes in S-T-T contour. With increase in the heart rate to 125 per minute immediately after exercise, the premature systoles disappeared, but recurred two minutes later when the rate had fallen to 111 per minute. No

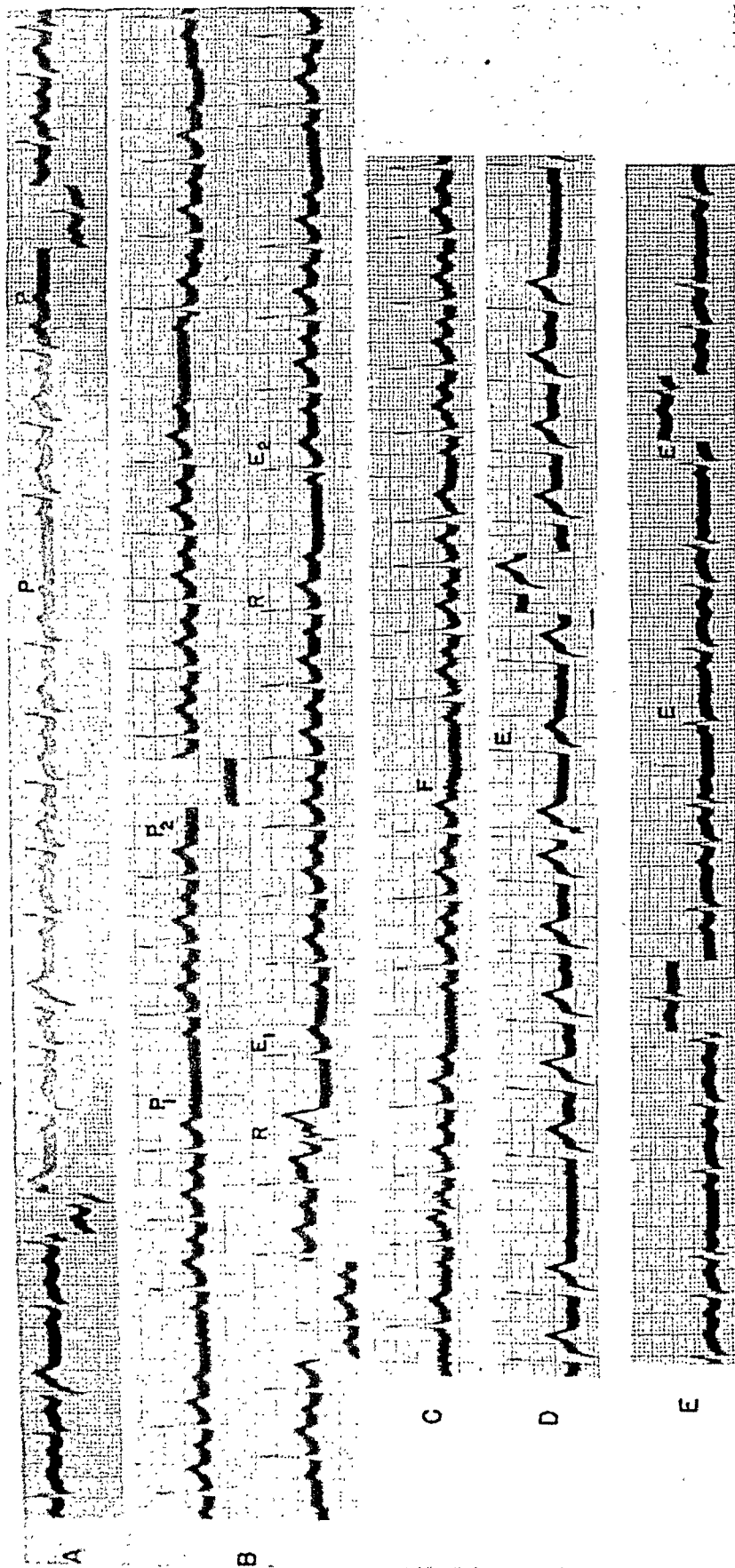


Fig. 2.—Blocked A-V nodal premature systoles initiating second degree A-V block. Discussed in text.

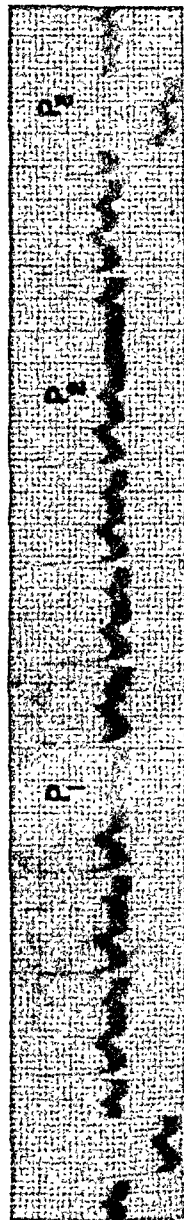


Fig. 3.—Blocked A-V nodal premature systoles initiating first and second degree A-V block. Discussed in text.

definite objective evidence of heart disease was discovered, and the patient's symptoms were thought to be in some manner related to the arrhythmia.

Fig. 2,A (Lead I) shows frequent premature systoles and, in addition, on two occasions a sinus P wave (marked P) which is not followed by a ventricular complex; there is no apparent disturbance preceding these sinus P waves to account for a failure of a ventricular response. Except for the very last beat which has a contour similar to that of the sinus beats all premature beats have a bizarre contour. They are not preceded by premature P waves. Variations in the preceding T wave which might suggest a superimposed premature P are due to a postextrasystolic change in contour of T. The coupling of those premature beats having bizarre ventricular complexes is fixed and is shorter than that of the premature systole having a nearly normal contour. At first, one might be inclined to assume that there are two types of premature systoles, ventricular and A-V nodal in origin, and, in addition, two instances of the rare type of A-V block characterized by "dropped beats" without the Wenckebach phenomenon. However, analysis of the other records (Figs. 2,B-E and 3) reveals that we are actually dealing with different manifestations of the same disturbance; namely A-V nodal premature systoles.

Fig. 2,E (Lead I, obtained several days after Fig. 2,A) shows further evidence for the occurrence of premature systoles of supraventricular contour. (The sinus P wave falling at the end of QRS of the premature beat should not be mistaken for a part of a widened QRS complex.) The third and fourth premature beats are followed by A-V nodal escapes (labelled E).

Fig. 2,B (Lead II, continuous strip; the last beat of the upper strip is repeated in the lower strip) shows on seven occasions a ventricular pause which is not preceded by a premature ventricular complex. The P wave, which occurs during the first portion of the long R-R interval and is not followed by a ventricular complex, can be identified in five instances as the sinus P wave occurring at the expected time and having the normal contour. In the two remaining instances (marked P₁ and P₂) P is inverted and perhaps slightly premature. These P waves are due to an ectopic impulse which is not conducted to the ventricles, or to fusion of such an impulse with the sinus impulse. The occurrence of A-V nodal premature systoles in other parts of the record would suggest that we are dealing not with blocked auricular but rather with blocked A-V nodal premature systoles with retrograde conduction (see Case 1). This is substantiated by the fact that an auricular premature impulse occurring as late in diastole as that of P₁ and P₂ would be expected to be conducted to the ventricles. The two instances where the sinus P wave is not followed by a ventricular complex, imitating a "dropped beat", and the analogous disturbances in Figs. 2,A, 2,C, and 2,D, can also be explained by the occurrence of A-V nodal premature systoles. Here, the sinus impulse giving rise to the "blocked" P wave interferes with a blocked A-V nodal premature systole (Fig. 4,C). The latter is actually blocked either in both directions or blocked only in a forward direction, whereas the retrograde impulse is prevented from invading the auricles by the interference of the normal sinus impulse.

Fig. 2,C (Lead II) shows a P₁ (marked F) which by its contour suggests a fusion of the sinus impulse with the retrograde impulse of the blocked A-V nodal premature systole; the same mechanism may account for the contour of P₁ in Fig. 2,B.

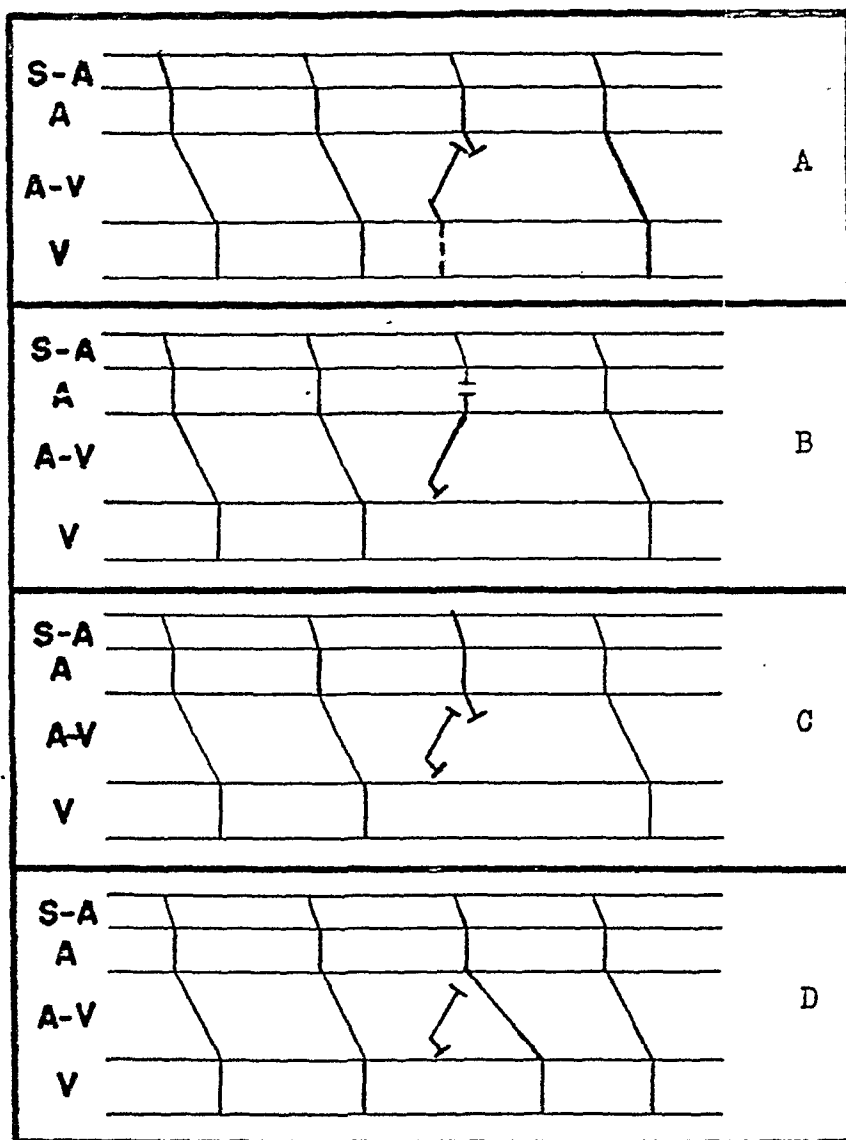


Fig. 4.—Diagram to illustrate the disturbance which can be caused by A-V nodal premature systoles. The conventions are those used customarily. A-V represents the spread of the impulse through the A-V junction between the auricles (A) and the ventricles (V). Blockage of an impulse is indicated by short lines at right angles to the oblique lines representing the impulse spread. The dashed line in A indicates aberrant conduction.

Segment A shows a nodal premature systole with aberrant conduction (imitating a ventricular premature systole). The retrograde nodal impulse is blocked before reaching the auricles.

Segment B shows a nodal premature systole with forward block (imitating a blocked auricular premature systole). The retrograde impulse interferes with the sinus impulse within the auricles, giving rise to a fusion P wave in the electrocardiogram.

Segment C shows a nodal premature systole with both forward and retrograde block (imitating second degree A-V block).

Segment D shows a nodal premature systole blocked (in both directions) and interpolated (imitating first degree A-V block).

This analysis of nonconducted sinus P waves as a result of blocked A-V nodal premature systoles with concealed conduction within the A-V junction is substantiated by another important detail. The two beats labelled E_1 and E_2 in the lower strip of Fig. 2, *B* are A-V nodal escapes, yet E_1 occurs at an R-R distance ($R-E_1$) which is much shorter than that of E_2 ($R-E_2$). This apparent difference can be easily accounted for by the occurrence of a blocked A-V nodal premature impulse preceding E_2 at a distance equal to $R-E_1$. E_1 follows the A-V nodal premature systole with aberrant conduction after the same time interval as E_2 follows an A-V nodal premature impulse, which, because of both forward and backward block, does not give rise to an electrocardiographic deflection. Another instance of an A-V nodal escape (labelled E) following a nodal premature systole with aberrant conduction is seen in Fig. 2, *D* (Lead CF_4). It follows the premature beat after the same time interval that E_1 follows R in Fig. 2, *B*.

Fig. 3 (Lead II) shows a phenomenon not seen in Fig. 2. On one occasion (P_1) there is a sudden prolongation of the P-R interval from 0.18 second to 0.36 second occurring without any change in the auricular rhythm. This can be explained by the same disturbance as the "dropped beats" present in Fig. 2 and occurring on two occasions in Fig. 3 (P_2 and P_3). A blocked premature A-V nodal impulse is responsible for the delayed conduction to the ventricles of the subsequent sinus impulse (P_1); since the latter is only delayed, but not entirely blocked, this is an example of a blocked and interpolated A-V nodal premature systole (Fig. 4, *D*). A slight prolongation of P-R of the beat subsequent to the impulse of P_1 (Fig. 3) is explained by the occurrence of the sinus impulse earlier in diastole of the preceding beat.

SUMMARY AND CONCLUSIONS

1. Two cases are reported with electrocardiographic evidence of blocked (nonconducted) premature systoles of A-V nodal origin occurring in individuals without definite evidence of cardiac disease.

- a. In Case 1 only forward conduction of the premature systoles is blocked whereas retrograde conduction is preserved. The diagnosis of blocked A-V nodal premature systoles is based on the retrograde contour of the premature blocked P waves and on the occurrence in the same record of typical conducted A-V nodal premature systoles with a shortened P-R interval. An A-V nodal premature systole with aberrant ventricular conduction presents a transition between the normally conducted nodal premature systole and that with forward block. Measurements of the coupling of the premature systoles and of the interextrasystolic P-P intervals suggest A-V nodal parasystole as the mechanism of the extrasystolic disturbance.

- b. In Case 2, A-V nodal premature systoles occur with block not only of forward conduction but also of retrograde conduction. Such blocked A-V nodal premature systoles can only be recognized by their effect on the subsequent sinus impulse. They lead either to a sudden P-R prolongation which cannot be accounted for by any other disturbance, or to a "dropped beat" without the usual preceding increase of the P-R interval. The former constitutes

a blocked and interpolated A-V nodal premature systole, hitherto undescribed in the human heart. The diagnosis of A-V nodal premature systoles blocked in both directions is based on the occurrence in the same record of typical A-V nodal premature systoles and of blocked premature P waves of retrograde contour. This analysis is substantiated by the presence of A-V nodal escapes, occurring with an apparent delay when they follow a "dropped beat."

2. A-V nodal premature systoles with retrograde conduction and forward block imitate blocked auricular premature systoles (Case 1).

3. A-V nodal premature systoles which are blocked in both directions imitate first degree or second degree A-V block (Case 2).

4. The disturbance caused by blocked A-V nodal premature systoles is further evidence of the effect of blocked impulses on the conduction of subsequent impulses.¹

We are indebted to Dr. D. A. Nathan of Miami Beach for his kindness in permitting us to use Case 1. We are also indebted to Dr. L. N. Katz for his criticisms.

REFERENCES

1. Langendorf, R.: Concealed A-V Conduction. The Effect of Blocked Impulses Upon Formation and Conduction of Subsequent Impulses, AM. HEART J.

CHANGES IN CARDIAC VIBRATIONAL INTENSITY IN RESPONSE TO PHYSIOLOGIC STRESS

JOHN H. FOULGER, M.D., PAUL E. SMITH, JR., M.A.,
AND ALLAN J. FLEMING, M.D.
WILMINGTON, DEL.

THE heart and adjacent aorta, in rhythmic contraction, relaxation, and movement within the thorax, continuously emit vibrational energy which can be detected and measured at the chest wall. This energy is distributed over a wide range of frequencies, including those audible vibrations termed the "heart sounds," but the major portion lies in frequencies below audible range. Rappaport and Sprague¹ point out that the intensity of low frequency vibrations picked up at the chest wall may be 10,000 times as great as that of the minimum audible vibrations (clinical "heart sounds").

The low frequency vibrations associated with heart action have been neglected in clinical research. Kountz and Wright,² studying cardiac vibrations with a cathode ray oscilloscope, noted that "low frequency systolic and diastolic waves developed under both clinical and experimental conditions and suggested . . . disordered cardiac function." In focusing attention on "disordered cardiac function," they overlooked the fundamental significance of these waves.

Research on cardiac vibrations, conducted in this laboratory for some five years by a number of experimental methods, has shown that low frequency vibrations are always produced in the cardiac cycle and that variations in frequency and particularly in the distribution of intensity over frequencies in these vibrations may be a valuable index of the response of the heart to physiologic loads placed on the total organism.

METHODS

The research program has necessarily been highly technical, employing a number of different methods of recording and analyzing heart vibrational intensity. Because we have studied a range of frequencies much lower than those usually considered, it has been necessary to examine the properties of several recording systems and to select those best suited to our immediate purpose, or to devise new apparatus. The principal methods of research have been:

Method A.—Spectra of cardiac vibrations were recorded by a frequency analyzer, used in conjunction with a Graphic Level Recorder.* The combined

From the Haskell Laboratory of Industrial Toxicology.

Received for publication Dec. 11, 1946.

*The frequency analyzer and the Graphic Level Recorder were made by Electrical Products Research Company.

apparatus traces vibrations at frequencies up to 10,000 cycles, the amplitude of the record being expressed in decibels. The cardiac vibrations are picked up at the chest wall by a dynamic microphone supplied with the apparatus.

This equipment was intended for routine measurements at frequencies much higher than those with which we are dealing. A check of the "linearity" of the recording apparatus shows complete loss of energy from 0 to 6 cycles per second, and marked loss between 6 and 18 cycles per second. This loss might be greater when the microphone is in the system.

Since, in making the tracing, the analyzer automatically scans the frequency range employed, the final record covers a number of cardiac cycles.

To simplify a study of records, the tracings obtained were integrated over six-cycle bands, using a photoelectric integrator specially designed for the purpose. The range of frequencies usually studied was 6 to 96 cycles per second.

Method B.—"Linear" records of human cardiac vibrations were made with the Sanborn Cardiette,* and the special sphygmograph attachment described by Rappaport and Sprague.¹ This attachment operates on the electrocardiograph channel. The conventional "heart sounds" were recorded simultaneously as an index of the duration of heart cycles. This apparatus gives tracings which are "linear" with respect to intensity from 0 to 50 cycles per second.

The photographic records obtained by this method were enlarged and carefully measured, and analyzed mathematically by the procedures described by Stumpff.^{3,4} Stumpff's system of harmonic analysis was chosen because frequent checks and counterchecks allow one to make tedious analysis without error. This is important, for even when a mechanical calculator is used, analysis of a single cardiac cycle may take from one-half a day to two days, depending upon the number of harmonics one wishes to disclose.

Method C.—Two simpler methods were devised for following changes in energy distribution among low frequency cardiac vibrations. One, which we term the "differential heart sound meter," was specially designed for routine work. Its operation does not require a high degree of skill.

Using these procedures, human subjects were subjected to physiologic "stress" by tilting, or by the Master 2-step exercise.⁵ Animals (dogs, rats, and guinea pigs) were exposed to chemicals which, by interfering with oxygen distribution to tissues, had virtually the same effect as exercise, though a more drastic one. The animal experiments recorded here are all based on exposure to carbon monoxide.

*Throughout this paper, the term "Sanborn Cardiette" refers to the special Sanborn Stetho-Cardiette with two channels

RESULTS

Method A. Cardiac Vibration Spectra of Man and Laboratory Animals.—

1. *At Rest:* Typical cardiac vibration spectra of man, dog, rat, and guinea pig at rest are shown in Fig. 1. Intensity in successive six-cycle bands between 6 and 96 cycles per second is plotted as per cent of total intensity from 6 to 96 cycles. The spectrum of man was made after ten minutes supine, since this position is most like the resting position of a four-legged animal, not requiring return of blood to the heart against gravity.

The animals used had been well fed and housed, and were accustomed to the little manipulation needed for this work.

For man and dog, the microphone was placed over the apex beat. For rat and guinea pig, it covered the whole heart.

Because of deficient recording of intensity at frequencies below 20 cycles per second, these spectra show peaks which are overemphasized. Actually, the maximum intensity lies at frequencies below 20 cycles per second as will be shown by later records obtained from Method B.

In the records obtained from man and dog, the major portion of intensity lies below 42 cycles per second. With an average heart rate of 84 per minute (1.4 cycles per second), this corresponds to the fundamental and harmonics up to the thirteenth. For rat and guinea pig, the major portion lies below 80 cycles per second. With an average heart rate of 200 per minute (3.3 cycles per second), this represents the fundamental and harmonics up to about the twenty-fourth.

2. *Changes of Cardiac Vibration Spectra of Humans When Subjected to Physiologic Stress:* It is obviously unwise to expose humans deliberately to noxious agents if other means of imposing stress are available. In man, such other methods can be either passive changes in posture or exercise. In what we term a "tilt test," our human subjects are placed supine on a stretcher held horizontal for five to ten minutes and then tilted to 45° from the horizontal with legs down. Fig. 2 shows a series of spectra obtained from such a test.

For convenience, the graphs indicate intensity distribution (per cent) above and below 42 cycles per second. Tilting immediately shifted intensity so that 37 per cent lay above 42 cycles, as compared with only 9 per cent in the control. Five minutes after tilting, 26 per cent was still above 42 cycles per second, indicating continuance of the physiologic load induced by the 45° position. Restoration to the horizontal was followed by a return almost to the control spectrum in five minutes.

The "tilt test" is predominantly a passive one, the change from horizontal to tilt position requiring a return of blood to the heart against gravity unaided by active muscular movement. (A certain degree of muscular movement was involved since our tilt table was not ideally constructed to take all load off the leg muscles when the subject was in the tilted position.)

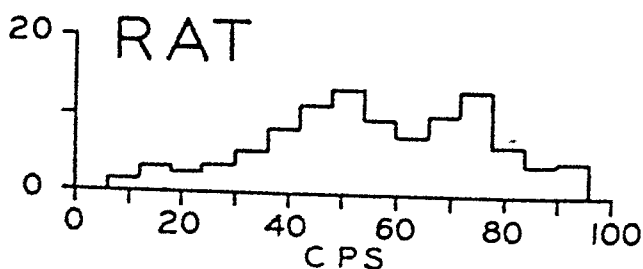
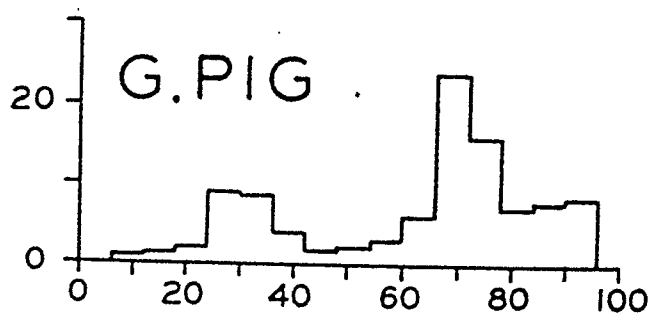
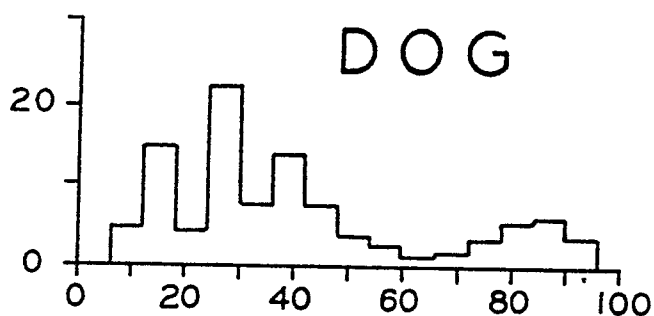
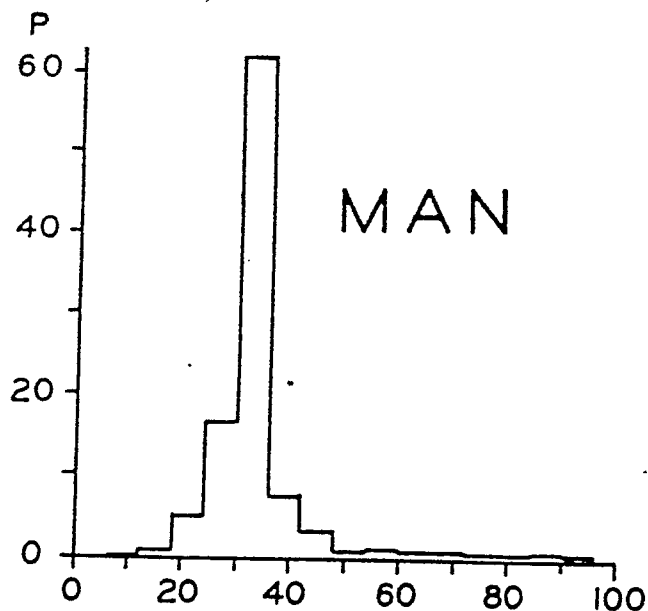


Fig. 1.—Typical distribution of cardiac vibrational intensity in man, dog, rat, and guinea pig, at rest. P = per cent of total intensity, 5 to 95 cycles per second, integrated over six cycle bands.

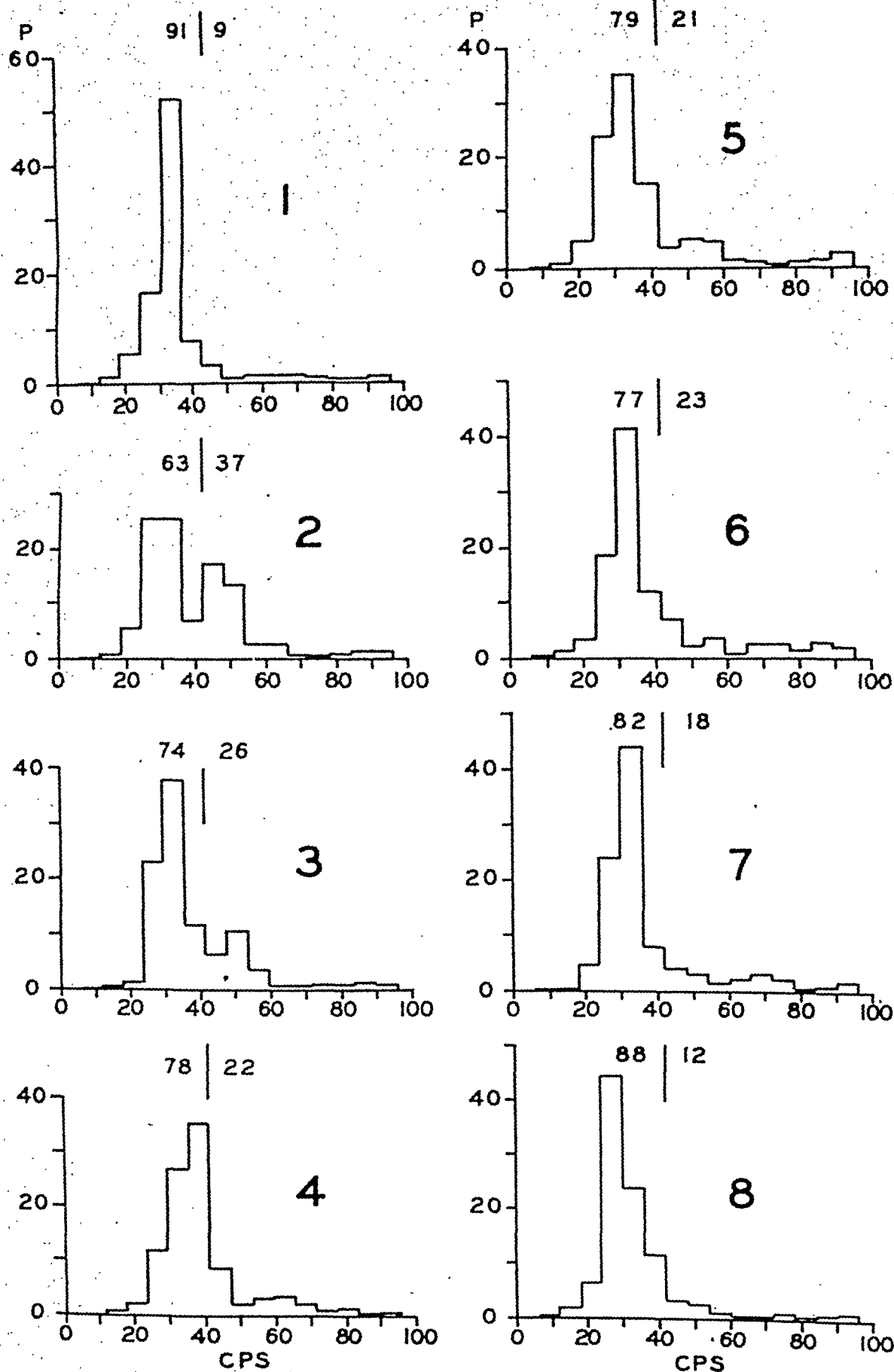


Fig. 2.—Influence of posture on distribution of cardiac vibrational intensity in man. P = per cent of total intensity, 6 to 96 cycles per second, integrated over six cycle bands. Numerals over each graph show distribution of total intensity about 42 cycles per second: 1—At end of 10 minutes horizontal; 2 to 5—Immediately, 1.5, 2.5, and 5 minutes after tilting to 45°. Subject remained tilted 8 minutes; and 6 to 8—at 2.0, 3.5, and 5 minutes after return to horizontal.

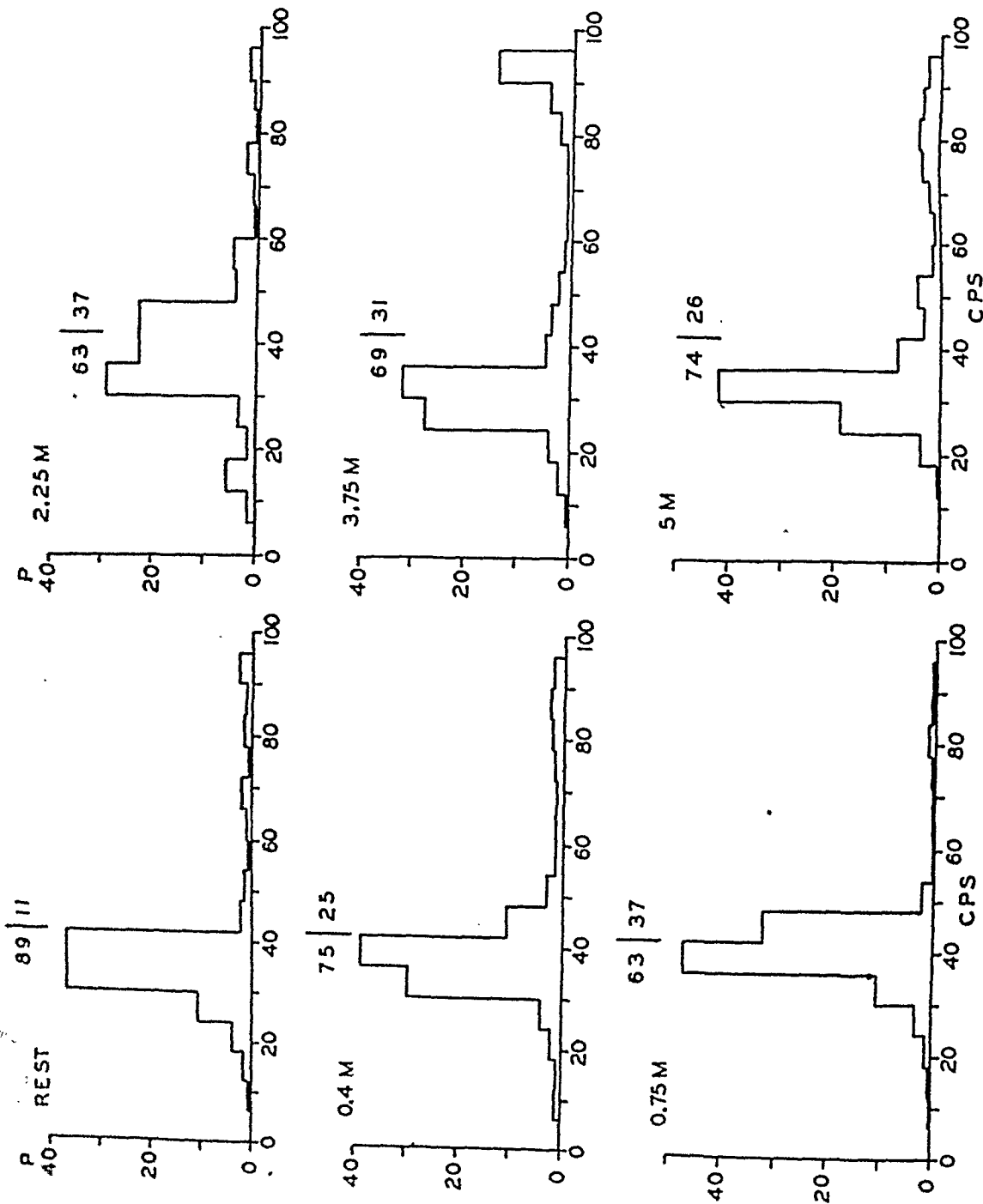


Fig. 3.—Influence of Master 2-step test on distribution of cardiac vibrational intensity. P = per cent of total intensity, 6 to 96 cycles per second, integrated over six cycle bands. Numerals over each graph show partition of intensity about 42 cycles per second. Graphs at rest (sitting) and 0.4, 0.75, 2.25, 3.75, and 5 minutes after end of exercise.

Fig. 3 shows spectra on the same subject obtained by the Master 2-step test. The control position was sitting. The exercise took one and one-half minutes. The subject then sat down at once. Such a test involves, first, assumption of a fully vertical position, and second, active muscular movement. This may impose a greater load than the tilt test. After five minutes sitting, the cardiac vibration spectrum showed 11 per cent total intensity above 42 cycles per second. At 0.4, 0.75, 2.25, 3.75, and 5 minutes after exercise, spectra (again taken in the sitting position) showed respectively 23, 37, 37, 31, and 26 per cent above 42 cycles per second. The immediate result of the exercise plus postural change was a shift of intensity to higher frequencies. Restoration to the control spectrum was not complete in five minutes.

3. *The Effects of Anoxia Produced by Inhalation of Carbon Monoxide:* Inhalation of carbon monoxide, converting hemoglobin to carboxyhemoglobin and thus reducing the oxygen-carrying capacity of the blood, leads to potentially the same results as exercise, since it demands greater minute uptake of oxygen to satisfy the tissues.

Figs. 4, 5, and 6 show vibration spectra on a rat, a guinea pig, and two dogs (*A* and *B*), exposed to carbon monoxide. In each case, exposure resulted in a definite trend in the intensity-frequency distribution. The different response of the two dogs is interesting. Henderson and Haggard⁶ state that "when the time of exposure is measured in hours and the concentrations of carbon monoxide are expressed in parts per million, the physiological effects may be roughly defined by the equation

"Time x Concentration = 300—No perceptible effects

"Time x Concentration = 600—A just perceptible effect

"Time x Concentration = 900—Headache and nausea."

In our experiments, for Dog *A*, Time x Concentration = 900; while for Dog *B*, Time x concentration = 340. Yet, Dog *A* was unaffected by exposure so far as could be determined by ordinary methods of observation, and showed a movement of vibration intensity to higher frequencies, while Dog *B* was prostrated by the exposure and showed a drastic shift of intensity to frequencies lower than in the control. The difference in response is quite probably due to the difference in the initial physiologic status of the two animals, *A* being quite well, while *B* was in poor condition and badly infested with worms. The immediate response of experimental animals or man to exposure to a toxic material depends definitely upon the physiologic condition in which the subject approaches the exposure.

Despite the deficiencies of the apparatus, the experiments cited clearly show a shift of cardiac vibrational intensity over the frequency range in response to physiologic stress and a tendency to return to control conditions when the stress is removed.

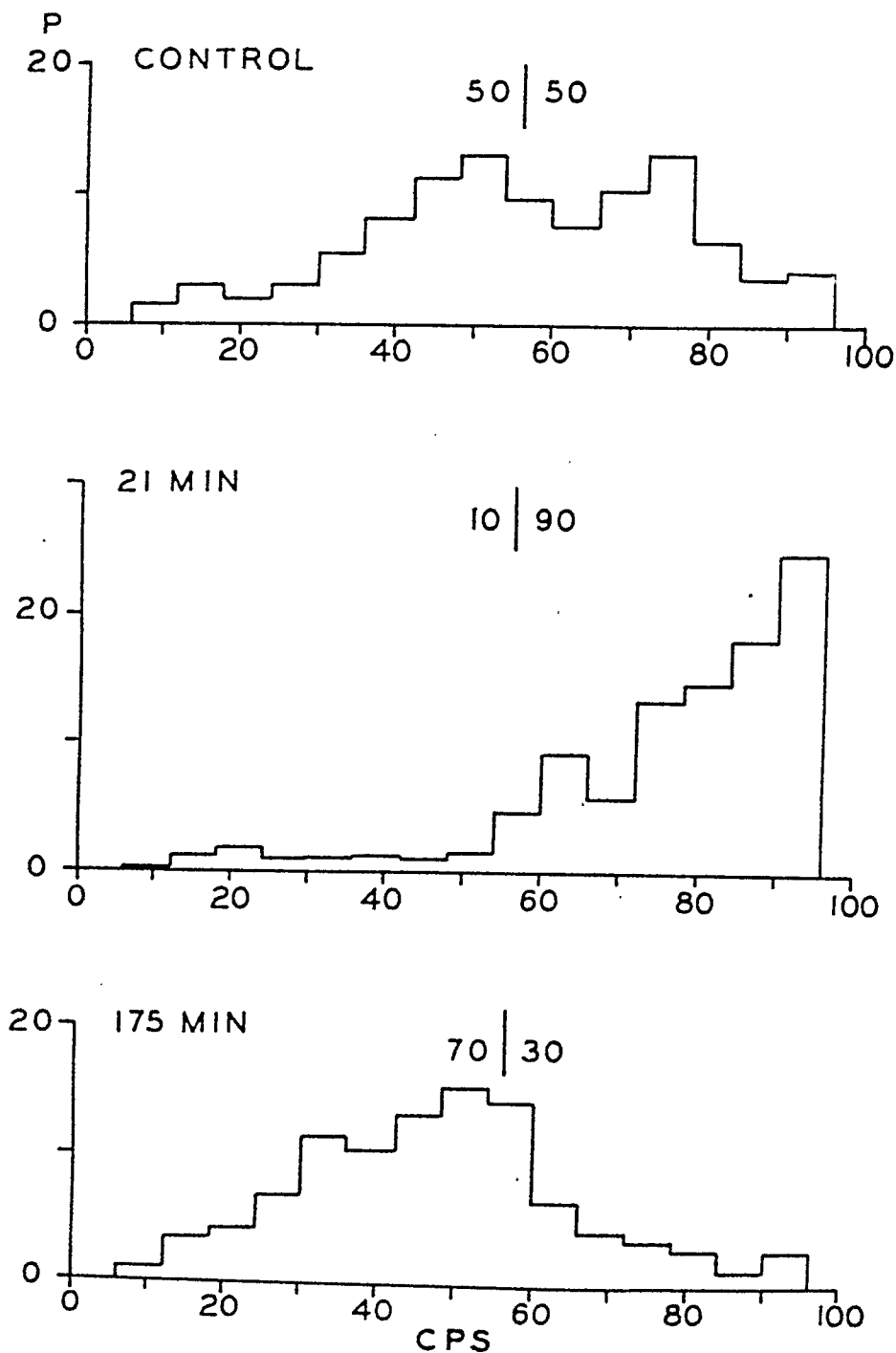


Fig. 4.—Influence of carbon monoxide (1,000 parts per million for 60 minutes) on distribution of cardiac vibrational intensity of rat. *P* = per cent of total intensity, 6 to 96 cycles per second, integrated over six cycle bands. Median frequency of control = 56 cycles per second. Graphs before and at 21 and 175 minutes after exposure ended. Note shift to higher frequency 21 minutes after exposure followed by depression below control distribution of intensity.

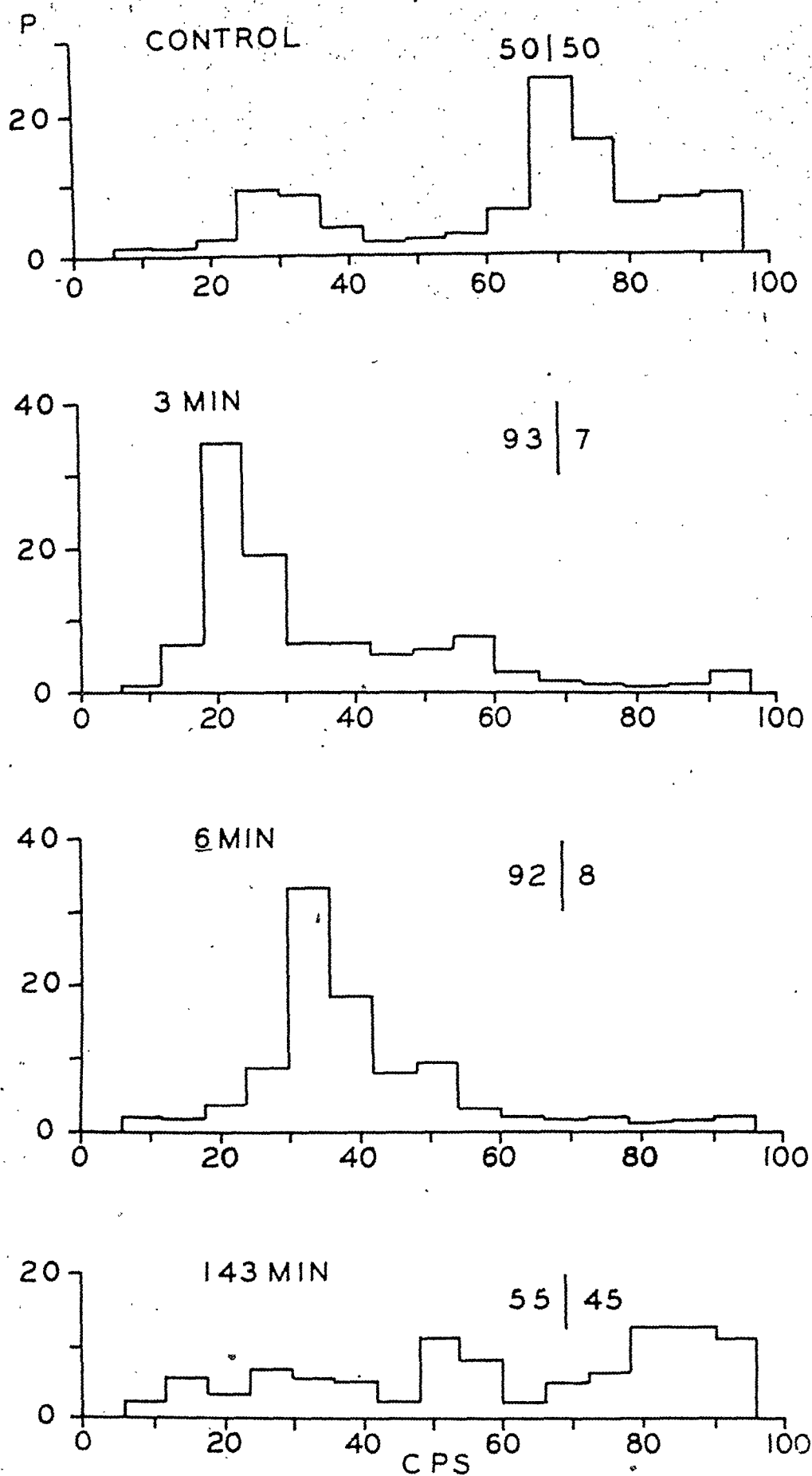


Fig. 5.—Influence of carbon monoxide (740 parts per million for 60 minutes) on distribution of cardiac vibrational intensity in guinea pig. P = per cent total intensity, 6 to 96 cycles per second, integrated over six cycle bands. Median frequency of control = 69 cycles per second. Graphs before and at 3, 6, and 143 minutes after end of exposure.

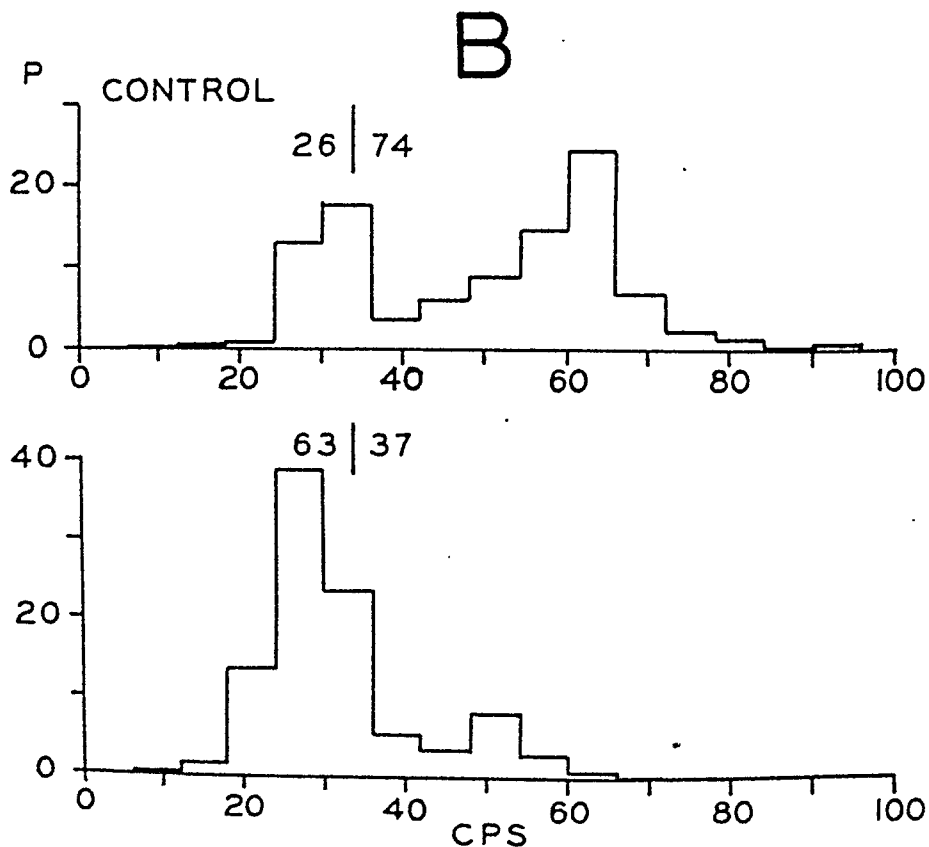
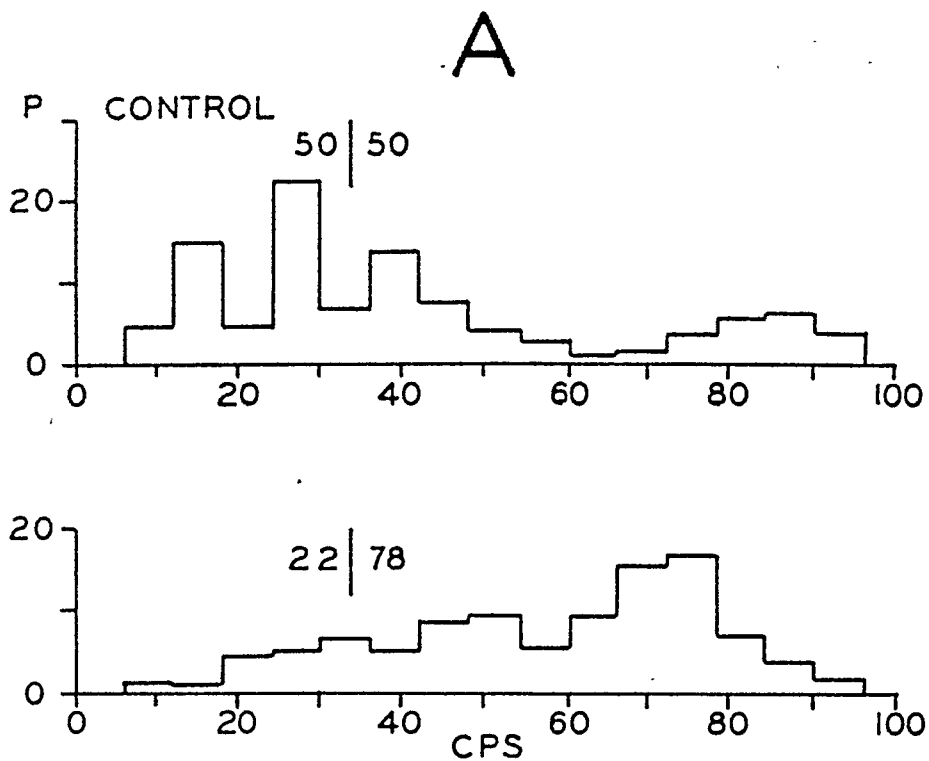


Fig. 6.—Influence of carbon monoxide on distribution of cardiac vibrational intensity in two dogs. *P* = per cent of total intensity, 6 to 96 cycles per second, integrated over six cycle bands. *A*, Before and immediately after 5 hours' exposure to 180 parts per million carbon monoxide. *B*, Before and 25 minutes after 32 minutes' exposure to 680 parts per million carbon monoxide. Numerals at top of graphs show partition of intensity about 34 cycles per second.

Method B. Analysis of "Linear" Records Made on the Sanborn Cardiette.—

Rappaport and Sprague¹ describe a special attachment for the Sanborn Cardiette with which "linear" records of cardiac vibrations can be made on the electrocardiograph channel. By the use of this equipment, it is possible to record the frequency region of 0 to 20 cycles, which is defective in the apparatus used in Method A. In recording heart vibrations with the Sanborn apparatus, we have used the conventional "heart sound" channel as an indicator of the period of successive heart cycles.

Photographic records were enlarged, and marked off into separate heart beats, extending from second sound to second sound as shown on the "heart sound" record. The period of each cardiac cycle was divided into 30 equal intervals, and the amplitude at the beginning of each interval measured with a Vernier calipers reading to 0.1 millimeter. The data so obtained were analyzed by the method of Stumpff^{3,4} to give the Fourier coefficients for the fundamental and fourteen harmonics, the fundamental being, of course, the frequency of the individual beat under study.

By harmonic analysis, the amplitude of a vibration record at any given instant is expressed as a Fourier Series

$$Y = a_0 + a_1 \cos \omega t + a_2 \cos 2\omega t + \\ + b_1 \sin \omega t + b_2 \sin 2\omega t +$$

in which

Y = amplitude at time t

a_0 is the average amplitude of the record over the cycle studied

a_1, a_2, a_3 , etc. = coefficients of the Cosine terms

corresponding to the harmonics present

b_1, b_2, b_3 , etc. = coefficients of Sine terms

$\omega, 2\omega, 3\omega$ = circular frequencies of the fundamental and harmonics.

This formula can be reduced to the equation, involving an average value a_0 and the sum of a series of cosines,

$$Y = a_0 + \sum A \cos (\theta t - x)$$

in which

$$A = \sqrt{a^2 + b^2}$$

θ = circular frequency of any harmonic present

x = phase displacement of the particular harmonic.

The Fourier amplitudes, A , represent the maximum instantaneous contribution of each frequency to the total amplitude of the tracing at any time during the beat. The sum of the coefficients will represent the maximum instantaneous amplitude subscribed by the fundamental and the first to fourteenth harmonics. Fig. 7 is a typical photograph of a Sanborn record of three heart beats.

1. *Changes in Cardiac Vibrations While at Rest:* Table I gives the Fourier amplitudes obtained by analysis of eight successive heart beats recorded with the subject supine, listing the fundamental frequency of each beat, and the coefficients of the fundamental and its harmonics in that beat.

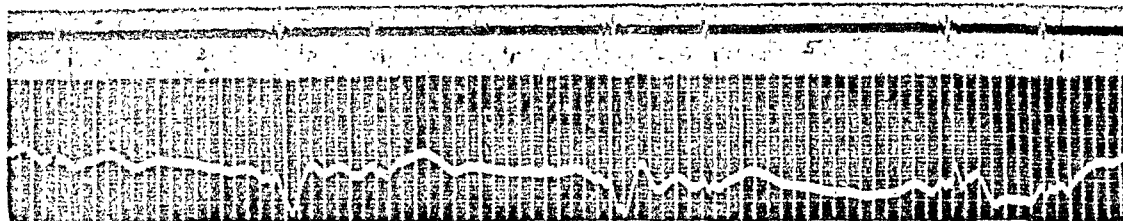


Fig. 7.—Photograph of records from Sanborn Cardiogram with conventional first and second heart sounds above, and linear record of vibrational intensity below. Three successive heart beats. Subject sitting.

(Analysis given in Fig. 10.)

The important features of this table are:

(a) In general, harmonics beyond the ninth contribute little to the total amplitude.

(b) There is a pronounced rhythmic change in the period of the beats and, therefore, in the fundamental frequency. The frequencies correspond to pulse rates varying between 64 (Beat 3) and 80 (Beat 5) per minute. This change occurs within a total time of 2.6 seconds.

(c) The total of coefficients of the fundamental and harmonics is also rhythmic.

For the present study, the shift of intensity over the frequency range is of major importance. This shift can be demonstrated easily by calculating the mean frequency of the Fourier coefficient distribution by the usual statistical method.

TABLE I. ANALYSIS OF EIGHT CONSECUTIVE HEART BEATS (PATIENT SUPINE)

BEAT	1	2	3	4	5	6	7	8
Period (second)	0.833	0.909	0.944	0.893	0.746	0.752	0.787	0.800
Frequency	1.20	1.10	1.06	1.12	1.34	1.33	1.27	1.25

Fourier Amplitudes (Unit 1 mm.)

Harmonic	1	2	3	4	5	6	7	8
1	0.96	0.99	1.61	2.64	2.07	1.11	0.74	0.89
2	2.22	1.14	1.34	1.74	1.53	2.38	2.17	2.41
3	1.14	1.98	1.56	1.08	1.15	0.75	1.10	0.47
4	2.25	1.07	0.64	1.51	1.95	2.36	2.25	2.28
5	1.70	2.07	1.83	1.59	1.15	0.97	1.67	0.99
6	0.40	1.22	1.14	0.74	0.66	0.35	0.28	0.70
7	0.31	0.38	0.52	0.84	0.14	0.29	0.24	0.06
8	0.19	0.32	0.43	0.16	0.26	0.06	0.14	0.17
9	0.25	0.11	0.56	0.40	0.20	0.08	0.20	0.23
10	0.17	0.15	0.09	0.09	0.36	0.03	0.07	0.23
11	0.08	0.00	0.05	0.26	0.10	0.12	0.13	0.11
12	0.12	0.08	0.09	0.18	0.32	0.30	0.09	0.10
13	0.13	0.13	0.02	0.20	0.21	0.24	0.05	0.11
14	0.07	0.20	0.11	0.29	0.19	0.06	0.06	0.09
15	0.07	0.10	0.12	0.11	0.14	0.04	0.03	0.11
Sum of coefficients	10.06	9.94	9.11	11.83	10.43	9.14	9.22	8.95

$$F = \frac{fA_1 + 2fA_2 + 3fA_3 + 4fA_4 + \dots}{A_1 + A_2 + A_3 + A_4 + \dots}$$

where f is the fundamental frequency and F the mean frequency.

Dividing throughout by f gives the formula

$$N = \frac{A_1 + 2A_2 + 3A_3 + 4A_4 + \dots}{A_1 + A_2 + A_3 + A_4 + \dots}$$

in which N is the mean harmonic. By this means, shifts in values of the Fourier amplitudes of harmonics can be disclosed independent of the actual fundamental frequency. It is obvious that any increase in N can result only from a relative increase in the amplitudes of frequencies higher than the fundamental, for an increase solely in A_1 would reduce the value of N .

Table II, summarizing the analysis of this record of eight heart beats, shows that both mean frequency, F , and mean harmonic, N , vary rhythmically while the subject is at rest.

TABLE II. TRENDS IN MEAN FREQUENCY AND MEAN HARMONIC DURING EIGHT SUCCESSIVE HEART BEATS (PATIENT SUPINE)

BEAT	1	2	3	4	5	6	7	8
N	4.20	4.61	4.29	4.45	4.50	4.09	4.06	4.25
F	5.04	5.07	4.55	4.98	6.04	5.44	5.16	5.32

To discover the source of this rhythm, a record of fifteen successive heart beats was made simultaneously with a record of the respiration. The respiratory tracing was made by a pneumograph activating a crystal microphone, which was, in turn, connected with a photoelectric recorder.* The signal systems of the Sanborn Cardiette and the recorder were connected so that they could be simultaneously activated by the signal plunger of the Cardiette. Fig. 8 shows the trend of respiration and the values of f , ΣA , N , and F for the fifteen successive beats, calculated over the range 0 to 20 cycles per second. No significance attaches to the absolute amplitude of the respiratory record, but the trend is important. The data charted in this figure are given in Table III.

The subject was sitting while the record was made. The average pulse rate was 102. (He was suffering from an acute sinus flare-up.)

There are a number of interesting points shown by Table III and Fig. 8.

(1) The period of successive heart beats shows minimal values toward the end of inspiration and is at its maximum during the expiratory pause. The fundamental frequency of each beat, of course, follows the inverse trend. However, the variation of frequencies is not wide.

(2) The sum of the Fourier amplitudes reaches a peak in general as inspiration changes to expiration and is lowest during the expiratory pause.

*General Electric.

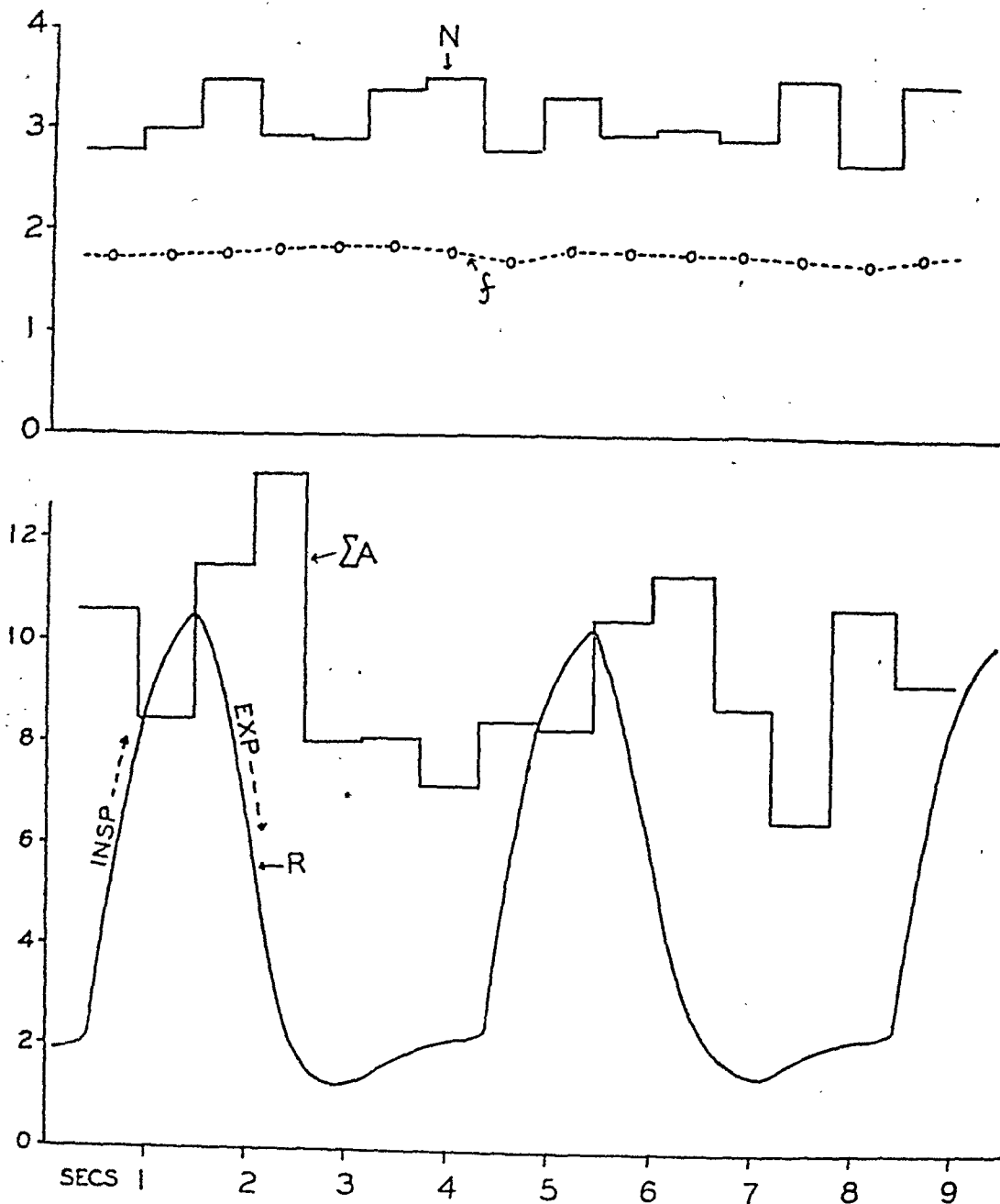


Fig. 8.—Analysis of fifteen consecutive heart beats correlated with respiratory cycle. Subject sitting. N = mean harmonic; f = frequency of each beat; ΣA = sum of Fourier coefficients; and R = respiratory cycle. (Drawn from data of Table III.)

(3) The mean frequency shows high values during inspiration but may also be high during the expiratory pause. The rhythmic variation of this mean frequency is much wider than the variation of the fundamental and is due to wide variation of the mean harmonic, N . N attains high values as inspiration changes to expiration.

TABLE III. ANALYSIS OF FIFTEEN CONSECUTIVE HEART BEATS (PATIENT SITTING).
CORRELATION WITH RESPIRATORY CYCLE

BEAT	PERIOD (SECOND)	f	SUM OF FOURIER AMPLITUDES 0 TO 20 C.P.S.	N	F	PHASE OF RESPIRATION
1	0.585	1.71	10.53	2.77	4.74	Beginning inspiration
2	0.581	1.72	8.44	2.98	5.13	Inspiration
3	0.568	1.76	11.46	3.46	6.09	End of inspiration and beginning expiration
4	0.559	1.79	13.22	2.93	5.24	Expiration
5	0.536	1.80	7.95	2.90	5.22	Expiratory pause
6	0.559	1.79	8.03	3.37	6.03	
7	0.571	1.75	7.11	3.49	6.11	
8	0.588	1.70	8.34	2.76	4.09	Inspiration
9	0.568	1.76	8.23	3.27	5.76	
10	0.571	1.75	10.46	2.91	5.09	Expiration
11	0.575	1.74	11.26	2.96	5.15	
12	0.575	1.74	8.64	2.88	5.01	Expiratory pause
13	0.592	1.69	6.38	3.44	5.81	
14	0.601	1.66	10.59	2.65	4.45	Inspiration
15	0.587	1.70	9.13	3.39	5.80	

2. *The Effect of Change in Posture:* The effect of a passive change in posture upon the intensity-frequency distribution of cardiac vibrations was studied by the tilt test. A series of successive heart beats was recorded after five minutes in the horizontal position, and at 15.4 seconds after tilting to 45°, with legs down. Each beat was analyzed, and f , N , and F calculated. Table IV gives the results.

TABLE IV. ANALYSIS OF GROUPS OF HEART BEATS BEFORE AND AFTER TILT TEST

BEAT		<i>P</i>	<i>f</i>	<i>N</i>	<i>F</i>	ELAPSED TIME (SECONDS)
1	After 5 minutes in horizontal position. Immediately before tilting	0.719	1.391	1.710	2.38	0.00
2		0.765	1.310	2.258	2.96	0.72
3		0.776	1.290	2.163	2.79	1.48
4		0.736	1.359	1.813	2.44	2.26
5		0.717	1.395	2.206	3.08	3.00
6		0.695	1.439	1.625	2.34	3.71
Mean				1.973	2.67	
ELAPSED TIME (SECONDS) AFTER TILTING						
7	Commencing 15.4 seconds after tilting to 45° with feet down	0.631	1.585	1.834	2.91	15.40
8		0.628	1.592	1.588	2.53	16.03
9		0.655	1.527	2.212	3.38	16.66
10		0.665	1.504	1.846	2.78	17.31
11		0.680	1.471	2.938	4.32	17.98
12		0.653	1.531	2.898	4.44	18.66
13		0.627	1.595	2.585	4.12	19.31
14		0.639	1.565	1.674	2.62	19.94
Mean				2.197	3.39	

The values of N and F varied during both the approximately four seconds of study when the subject was horizontal, and the 4.5 seconds while tilted, but at 18 seconds after tilting N and F attained values much higher than those recorded in the horizontal position. The mean values of N and F for each complete series are obtained from values of A for all frequencies involved.

3. *The Effect of Exercise:* Records were made on a subject before and immediately after performing the Master 2-step exercise. The subject was sitting while all records were made. Groups of five or six successive heart beats were analyzed for the pre-exercise period, and at intervals of approximately 20, 29, 40, 60, and 75 seconds after exercise ended. For each beat, the mean frequency was calculated over the range 0 to 20 cycles per second. The value of N is shown in the graph of Fig. 9, together with mean values of N for each series of heart beats.

There was considerable variation in N during the two study periods. Twenty seconds after exercise ended, N was less variable and the mean value of N for this and the next two succeeding groups of heart beats was above the control

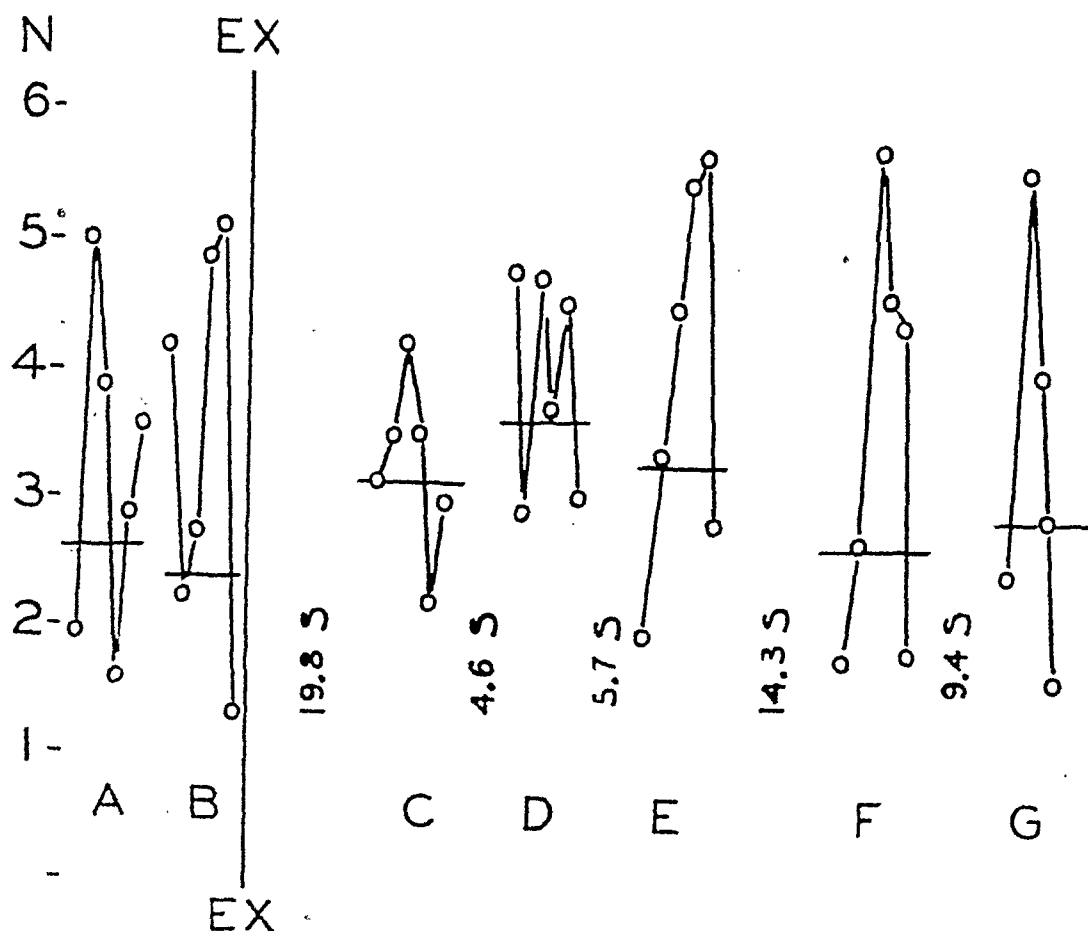


Fig. 9.—Variations of mean harmonic N and average N for groups of six heart cycles. A, B: Before Master 2-step test; and C, D, E, F, G: at intervals after test. Numerals between groups of N values show time elapsed since last beat analyzed.

value. At 59.6 seconds and 74.6 seconds increased variability of N appeared with a drop in the mean values for the groups.

Analysis of records obtained by Method B, therefore, shows the same phenomena as Method A; namely, a shift of distribution of intensity over the frequency range in response to physiologic load, with a return toward control conditions on removal of the load. Under Method B individual cardiac beats were considered, demonstrating trends not detectable by Method A, in which the automatic recorder averaged over a series of beats. Further, this method covered the range of 0 to 20 cycles per second deficient in the records of Method A, and showed that these low frequencies actually contribute the greater part of the intensity of cardiac vibration, yet show trends of the same type as detected by Method A for the range of 20 to 100 cycles per second.

The Cause of Changes in the Intensity-Frequency Distribution Shown by Methods A and B.—By dividing records of single heart beats into submultiples and analyzing each, trends in the intensity-frequency distribution can be disclosed during each individual beat. Fig. 10 shows a tracing of a "linear" vibration record of three successive heart beats made with the subject sitting. Each beat is divided into six equal parts and the spectra of Fourier coefficients, A , and the corresponding values of N are shown for each one-sixth cycle.

From general principles the intensity-frequency distribution of vibrational activity during a heart beat should be related either to the intraventricular pressure or to the ventricular volume, which, in physiologic discussions, is considered a measure of the length of the muscle fibers. The variations of N in Fig. 10 do not appear to follow either intraventricular pressure or ventricular volume trends as these have been disclosed by the work of Wiggers and Katz.⁷ But if one remembers that an increase in N denotes a relative shift of intensity to higher harmonics, and vice versa, and combines this fact with the statement made by Lamb⁸ (in connection with vibrations of a string on impact) that "according to a general principle . . . the higher harmonics are excited in greater relative intensity the more abrupt the character of the originating disturbance," it seems logical to suggest that "the originating disturbance" is a change in the length of ventricular muscle fibers, that is, a change in ventricular volume, and that the "abruptness" of this disturbance is represented by the rate of change of ventricular volume. The simplest conclusion is that N is directly proportional to the rate of change of ventricular volume. If the values of N from section to section of the three heart beats of Fig. 10 be summed with N taken as positive from second to first sound and negative from first to second sound in accordance with the direction of changes in ventricular volume, the graph SN is obtained, as shown at the bottom of Fig. 10. This graph is very similar to the known curve of ventricular volume changes.

If, for the moment, it be accepted that N is proportional to the rate of change of ventricular volume, that is, $N = K \frac{dV}{dt}$, general mathematical and physical considerations lead to an interesting result. N is a mathematical function, $g_1(I)$, of the vibrational intensity. But intensity is rate of change of energy,

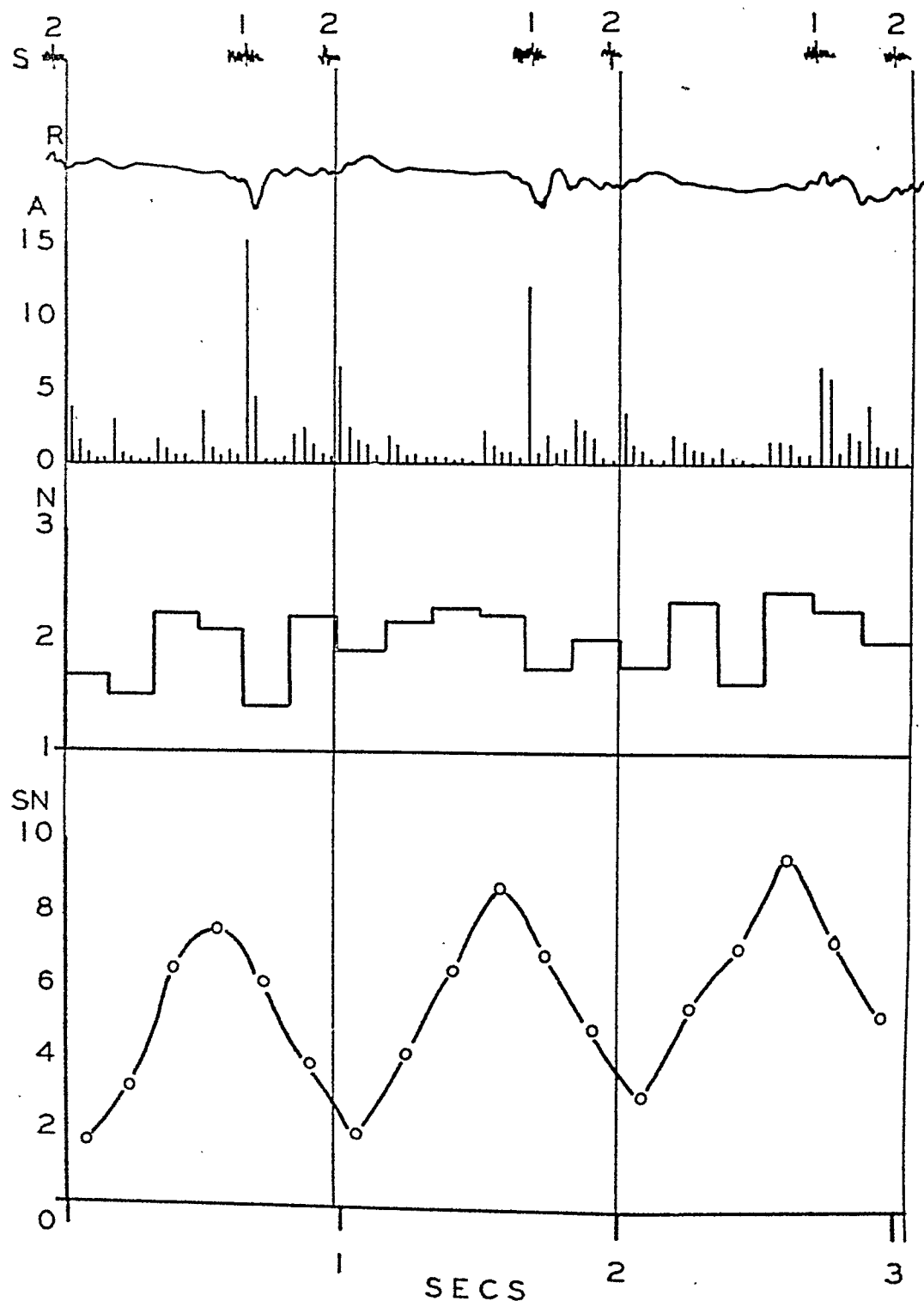


Fig. 10.—Analysis of three heart beats shown in Fig. 7. *S*—First and second heart sounds; *R*—tracing of record on Sanborn cardiograph; *A*—spectra of Fourier coefficients for each one-sixth beat; *N*—value of mean harmonic for each one-sixth beat; and *SN*—sum of *N*, with *N* positive from second to first sound, and negative from first to second sound.

$\frac{dE}{dt}$. Hence, if N is proportional to the rate of change of ventricular volume,

we have the argument $N = g_1(I) = g_1\left(\frac{dE}{dt}\right) = K \frac{dV}{dt}$ whence energy is a function of ventricular volume, that is, $E = g_2(V)$. Starling's "Law of the Heart" states that "the energy set free at each contraction of the heart is a simple function of the length of the fibers composing its muscular walls." The energy of vibration must be part of the total energy set free, and hence must also be a function of the length of muscle fibers (that is, of ventricular volume). Thus, our suggested relationship between the mean harmonic, N , of the intensity-frequency distribution is in conformity with Starling's "Law of the Heart."*

The laborious procedures of analyzing records used in Methods A and B are not suitable for routine study of cardiac vibration. More facile apparatus will be described. However, it is of value at this point to consider factors which might affect ventricular volume, in light of the physiologic loads which have been shown previously to influence the distribution of intensity of vibration.

*Our suggested relationship between the relative intensities of higher harmonics of vibration frequency during the heart cycle and the length of the ventricular muscle fibers conforms also to physical laws. If a stretched string of length, L , is deformed by a disturbance operating for a time, ϕ , the intensities of the higher harmonics are proportional to

$$\frac{-2\pi c s \phi^2}{e L}$$

where $c = \sqrt{\frac{\text{tension}}{\text{density}}}$

s = harmonic number

ϕ = duration of operation of disturbance

L = length of string

Assume that in the heart, the "originating disturbance" is the change in length of ventricular fibers. The duration of action of this disturbance, ϕ , over any very small period of the cardiac cycle will be dl/dL , the time required for a small change in fiber length. As diastole changes to systole, there is little change in L and, therefore, ϕ approaches infinity. During systole, ϕ will decrease and then increase in accordance with the downslope of the ventricular volume curve. As systole ends and diastole begins, ϕ again approaches infinity. As the ventricle fills with blood, ϕ will follow the upslope of the volume curve.

The relative intensity of a given higher harmonic, s , being proportional to

$$\frac{-2\pi c s \phi}{e L}$$

will be greater when $2\pi c s \phi / L$ is small, and vice versa. When ϕ approaches infinite values, the relative intensity will be small no matter what the value of L . As ϕ diminishes and L increases, the relative intensity of this harmonic will increase.

In our preceding analysis, the mean harmonic, N , is calculated from

$$N = \frac{A_1 + 2A_2 + 3A_3 + 4A_4 + \dots}{A_1 + A_2 + A_3 + A_4 + \dots}$$

where A_1, A_2, A_3 , etc., are the Fourier amplitudes of the harmonic components of the complex cardiac vibrations. Using the formula for relative intensities of harmonics, in place of A_1, A_2 , etc., and giving s the values 1, 2, 3, etc.,

$$N = \frac{\frac{-2\pi c \phi}{e L} + 2e \frac{-4\pi c \phi}{L} + 3e \frac{-6\pi c \phi}{L} + \dots}{\frac{-2\pi c \phi}{e L} + e \frac{-4\pi c \phi}{L} + e \frac{-6\pi c \phi}{L} + \dots}$$

(Footnote continued on next page.)

The volume of the ventricle depends upon the quantity of blood in it. This is determined during systole by the rate of ejection through open aortic and pulmonary valves. The rate of ejection in turn is controlled by the physiologic condition of the heart muscle. During diastole the volume of the ventricle depends upon the venous inflow, which in turn is influenced by posture, the respiratory cycle, the tonus of muscle of the abdominal wall and lower extremities, and the condition of the peripheral capillary bed. During diastole the rate of venous return will be increased by inspiration. After exercise it should, under normal conditions, be increased by additional tonus of skeletal muscle in the abdominal wall and lower extremities and by peripheral vasoconstriction. During expiration or under a condition of low muscle tonus or peripheral vasodilation, the rate of venous return should fall. The supine position, by eliminating the effect of gravity, should improve venous return. A change in posture from the horizontal should be compensated quickly by adjustment of venous return. During systole the rate of ejection of blood from the ventricle, which controls the rate of change of ventricular volume, should be increased by exercise, either as a result of increased diastolic filling or increased tension of the cardiac muscle. The rate of ejection should be diminished by an excessive load, anoxia, chemical poisoning, disease of the myocardium, and, perhaps, by increased peripheral resistance to blood flow.

Dividing through by $e^{-2\pi c\phi/L}$, this becomes

$$\begin{aligned}
 N &= \frac{1 + 2e^{\frac{-2\pi c\phi}{L}} + 3e^{\frac{-4\pi c\phi}{L}} + \dots}{1 + e^{\frac{-2\pi c\phi}{L}} + e^{\frac{-4\pi c\phi}{L}} + \dots} \\
 &= \frac{\frac{-2\pi c\phi}{L} - 2}{(1 - e^{\frac{-2\pi c\phi}{L}})} \\
 &= \frac{\frac{-2\pi c\phi}{L} - 1}{(1 - e^{\frac{-2\pi c\phi}{L}})} \\
 &= \frac{1}{1 - e^{\frac{-2\pi c\phi}{L}}}
 \end{aligned}$$

When ϕ becomes infinitely great, $N = 0$; when $\phi = 0$, N is infinitely great; that is, $N = K/\phi$. But

$$\phi \approx \frac{dt}{dL}. \quad \text{Hence, } N = K \frac{dL}{dt} = K \frac{dV}{dt}.$$

This physical concept may even have a wider application to successive complete heart beats. If we assume that the "originating disturbance" is the beat itself, its duration, ϕ , will be the period of the beat. If in two or more successive beats the average ventricular volume, $V = L$, remains the same, the relative intensities of a given higher harmonic, s , will be proportional to $e^{-\phi}$. As ϕ increases (that is, as the period of the beat increases), the higher harmonics will occur with less and less intensity. A short, snappy heart beat should give a vibration spectrum with greater intensity of higher harmonics than a long beat. Further, in the limit, a dying heart or a badly diseased heart with poor function should, as Kountz and Wright² reported, give a vibration spectrum in which "low frequency diastolic and systolic waves" appear with pronounced intensity.

These factors increasing or decreasing the rate of change of ventricular volume during the heart beat should also decrease or increase the value of N . Experiments already cited demonstrate the expected changes of N during inhalation and exhalation, in response to changes in posture, and exercise, and to a chemical poison, carbon monoxide. With suitable apparatus, therefore, a study of low frequency cardiac vibrations may add much to our knowledge of cardiodynamics in people apparently well and at work.

Method C. Simple Apparatus for Study of Low Frequency Cardiac Vibrations.—The mean frequency, N , of the intensity-frequency distribution of cardiac vibration was calculated mathematically by "weighting" the Fourier amplitude of each frequency component by its harmonic number. If a physical means could be devised for weighting the instantaneous contribution of each component frequency of the vibrational spectrum, an apparatus could be constructed to demonstrate and measure changes during a heart beat or a succession of beats. Such a physical means exists in the sound "filter". A "low-pass" filter passes less and less of the signal presented to it as the frequency of the signal increases. A "high-pass" filter behaves in the reverse fashion. Fig. 11 shows the output as per cent (P) of input of a typical low-pass filter (L), a high-pass filter (H), and the ratio (C) of high-pass to low-pass output when a single frequency is applied.

If the signal of heart vibrational intensity, picked up at the chest wall, is presented to these two filters, and if L represents the low-pass output; a_1, a_2, a_3 , the instantaneous contribution of successive harmonics to the total signal; $L(f), L(2f), L(3f)$, etc., the fraction of input passed at the fundamental frequency, f , and its harmonics, then $L = a_1L(f) + a_2L(2f) + a_3L(3f) + \dots$. Similarly, if H is the output of the high-pass filter, and $H(f), H(2f), H(3f)$, etc., the fraction of input passed for f and its harmonics, $H = a_1H(f) + a_2H(2f) + a_3H(3f) + \dots$.

The ratio of the two outputs will be

$$R = \frac{a_1H(f) + a_2H(2f) + a_3H(3f) + \dots}{a_1L(f) + a_2L(2f) + a_3L(3f) + \dots}$$

This ratio, R , will have a numerical value which can be varied between 0 and 1 by suitable selection of the filters. If multiplied by 100, $100 R$ could assume the values of P for curve C of Fig. 11 and have the properties:

1. $R = 50$ at 10 cycles per second, and 100 at 20 cycles per second.
2. R increases linearly with frequency, each unit frequency increase producing an increase of 5 per cent in the value of R .

While R would be produced, in the signal from the heart, by summation of instantaneous contributions from many frequencies, the same value could also be attained by presenting a signal at a single frequency to the filter system. Thus, by the filter system, the complex signal can be expressed in terms of a single "resultant" frequency analogous to the mean harmonic, N . Further, since R is a ratio, the absolute intensity of the original signal will, within practical limits, not affect the value of R .

Using such a system of filters, two pieces of apparatus have been constructed for demonstrating and measuring shifts in the intensity-frequency distribution

of cardiac vibrations. In each case, the signal from the microphone is amplified and passed to a low-pass and a high-pass filter of properties similar to those shown in Fig. 11. The output of the filters is employed in two ways:

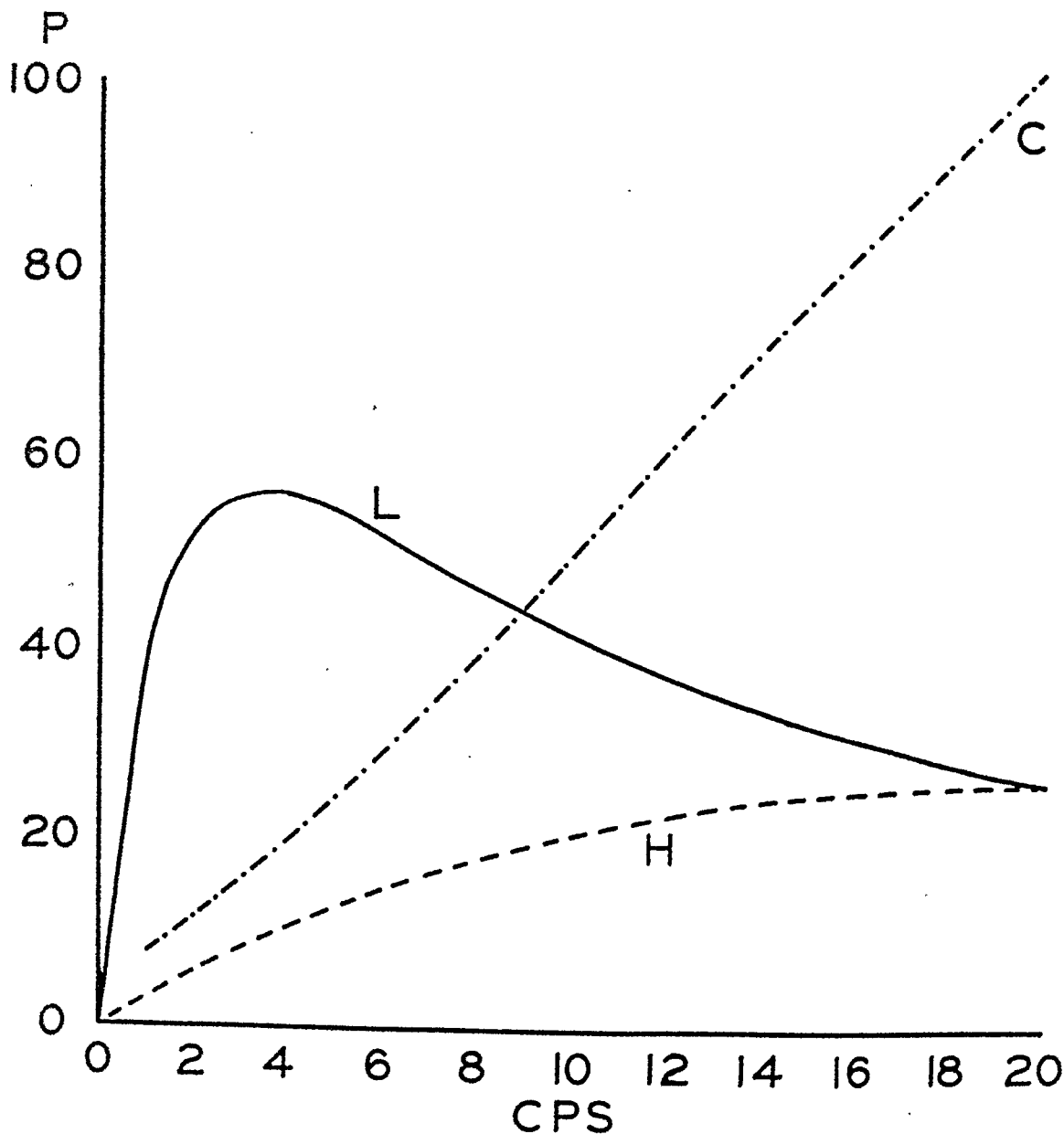


Fig. 11.—Curves of output as percent (P) of input for typical: L —low-pass filter, H —high-pass filter, C = ratio of output H/L .

1. *For Demonstration With a Cathode Ray Oscilloscope:* The filters are connected to two poles of a double pole, double throw, vibrating switch. The vibrating arm is connected with the vertical input of a cathode ray oscilloscope. The remaining two poles of the switch are connected to the synchronizing channel of the oscilloscope. The switch, vibrating at 120 cycles per second, alternately picks up the output from low- and high-pass filters. Each output appears as a

horizontal bar of light on the viewing screen and the two bars can be made to move up and down against a vertical arbitrary scale. As used, the output of the low-pass filter lies to the right of the scale and that of the high-, to the left. For the experiments shown in Fig. 12, the two were balanced at the zero point

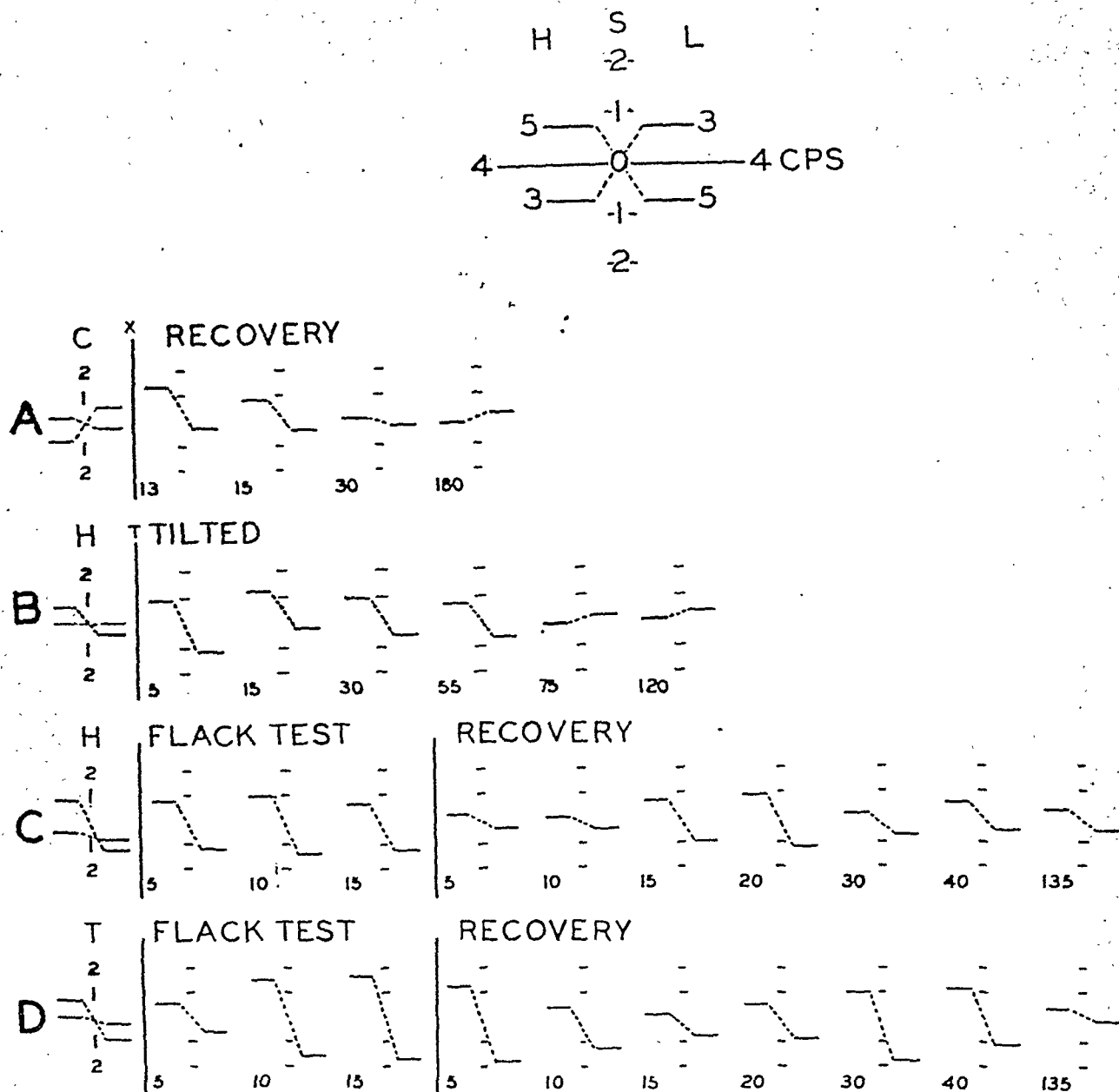


Fig. 12.—Oscillograph patterns from differential heart sound meter in A—exercise test; B—tilt test; C—Flack test while supine; and D—Flack test while tilted to 45°.

Diagram at top of figure shows standardization S = center scale; H = output of high-pass filter; L = output of low-pass filter.

Controls shown to left of vertical lines: A, control C—subject sitting; B, control H—subject horizontal 5 minutes; C, control H—subject horizontal 5 minutes; and D, control T—subject tilted 5 minutes.

of the scale with a signal of 4 cycles per second. At 5 cycles per second, the high-pass line moved upward; the low-pass, downward. At signals of lower frequency than 4 cycles per second, the movement was reversed. The oscilloscope pattern was photographed during a group of tests using a cinematograph camera at 16

frames per second. From the negatives, individual frames were projected and copied to give the diagrams of Fig. 12, in which

- A = exercise test (C = control, sitting)
- B = tilt test (H = control, supine)
- C = Flack test while horizontal (H = control)
- D = Flack test while tilted to 45° (T = control).

In each case, a movement of either output beyond the control range indicates a shift in intensity-frequency distribution and the spread between the high- and low-pass bars shows the extent of the shift.

In the Flack tests, it is noteworthy that the spread was greater when the subject was at 45° than when he was supine. He remarked that the test was a much greater physical strain while tilted than while lying.

2. *The Differential Heart Sound Meter:* For routine study of cardiac vibrations, the output of the filters is passed to a suitable diode voltmeter which includes a potentiometer and a galvanometer. The galvanometer may be of the simple needle type with a scale or a recording instrument such as the Photoelectric recorder.

When the simple galvanometer is used, the galvanometer needle oscillates from side to side of the scale during each heart beat and the operator adjusts the potentiometer by means of a dial graduated from 0 to 100, so that the oscilla-

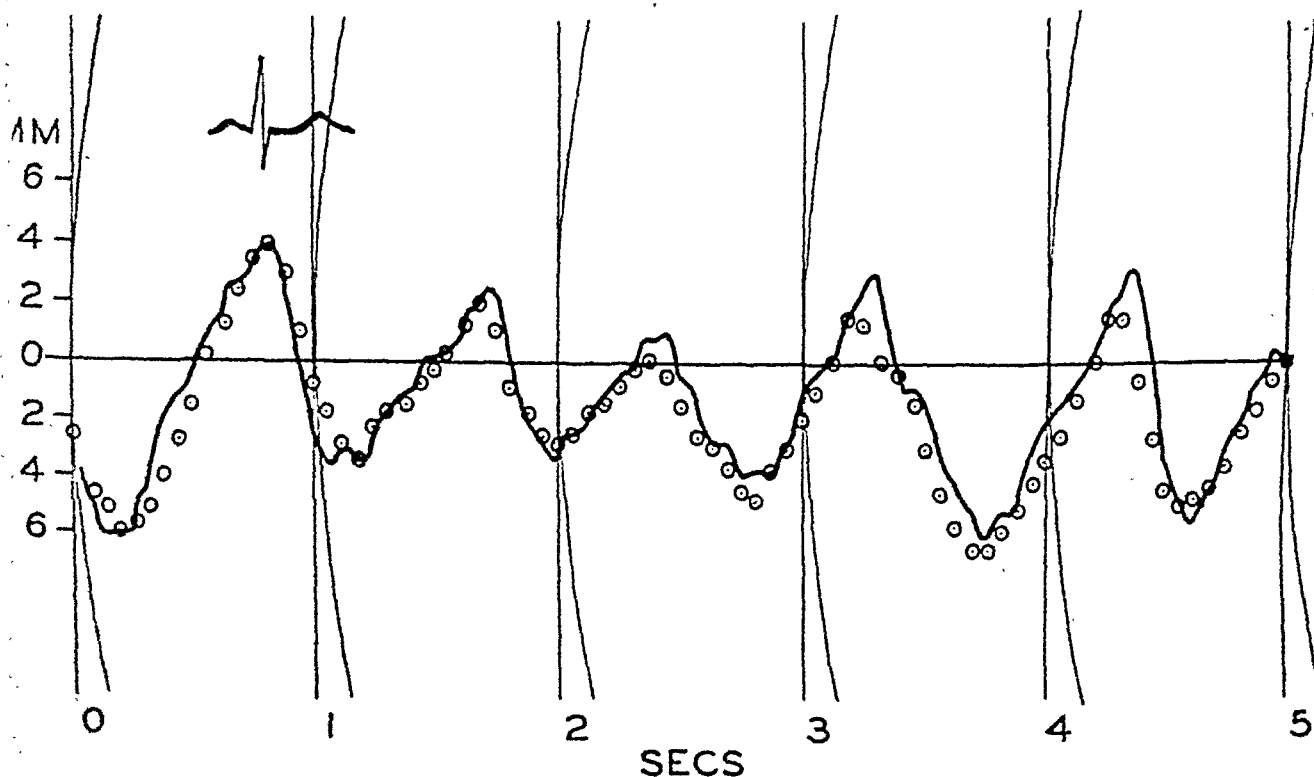


Fig. 13.—Full line—photoelectric recorder tracing of differential heart sound meter output. Curvilinear time markings. Circles—position of galvanometer needle on differential heart sound meter synchronized with direct record. Vertical time markings. Timing of deflections of ECG. Lead II, shown diagrammatically. Vertical axis shows deflection (in mm.) from balance point of meter.

tions show equal excursions on either side of the central zero of the scale. During a test the dial at balance is read every thirty seconds.

When a recording instrument is used the potentiometer dial is set at a point which is suited to the scale of the recorder.

In Fig. 13, a record made on the photoelectric recorder (full line) is compared with simultaneous movements of the simple galvanometer needle (circles). The latter was photographed at 16 frames a second and measurements made from successive frames. The curvilinear time axes are those for the recorder, spaced five-sixths of a second apart. The vertical time axes are for the galvanometer needle readings. Each is measured in millimeters from the balance point. Above the first heart beat the deflections of the electrocardiogram (Lead II) are shown diagrammatically with the same time relationship as appeared on the original record. Obviously, there is no appreciable difference between the records obtained by the two methods. Further, the excursions during each heart beat are comparable in trend and timing to the known changes in ventricular volume.

In Fig. 14 are shown photographs of three records taken with the photoelectric recorder: *A*, after lying five minutes; *B*, after sitting five minutes; and *C*, after standing two minutes. At the lower part of each are shown the

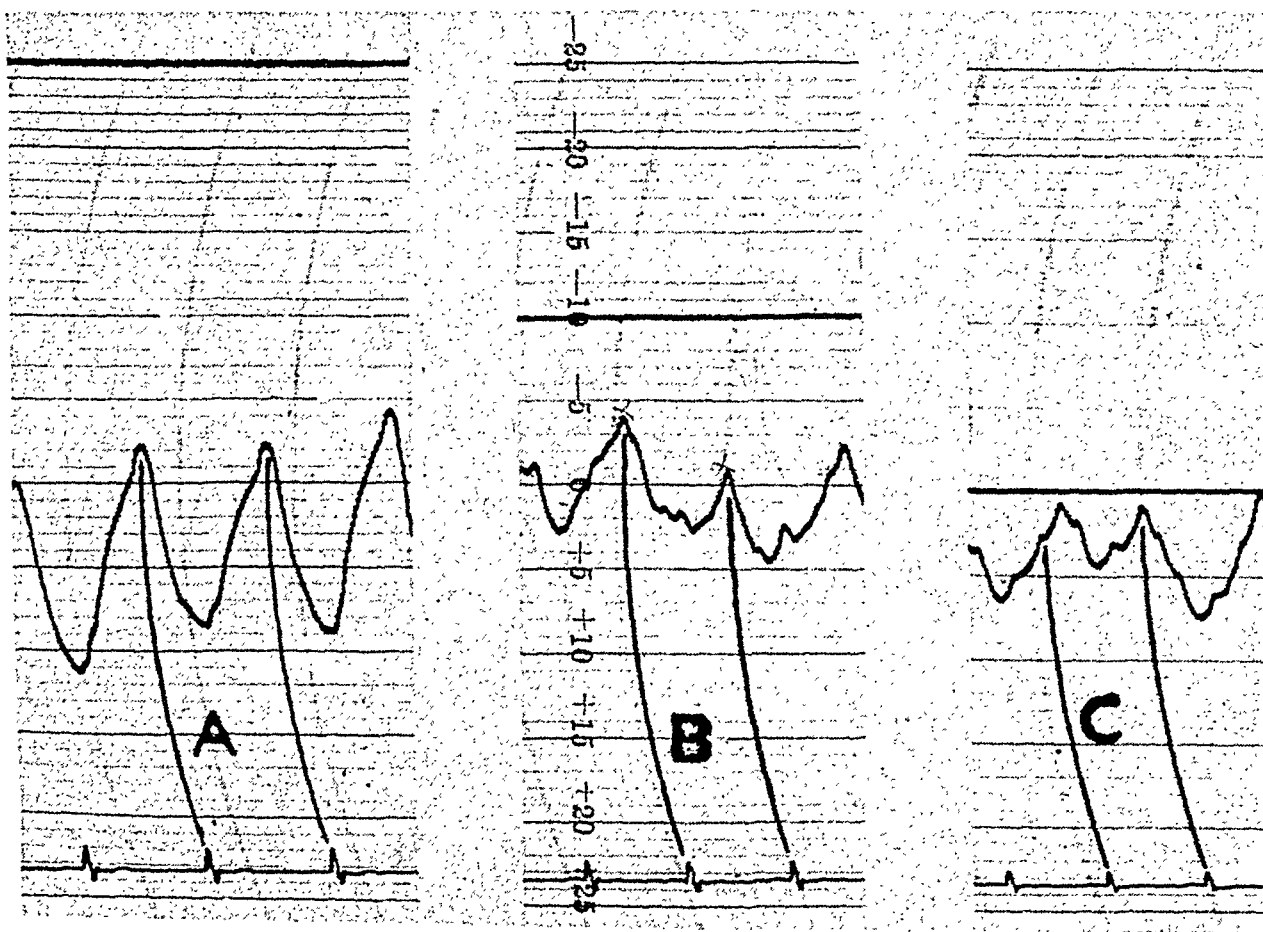


Fig. 14.—Photograph of photoelectric record from differential heart sound meter: *A*, after 5 minutes supine; *B*, after 5 minutes sitting; and *C*, after 2 minutes standing. Heavy horizontal line shows balance of meter at 10 cycles per second. Each small vertical interval is equivalent to 0.2 cycle per second. Lead II of ECG, synchronized with meter record.

major deflections of Lead II of the electrocardiograph, recorded directly on the recorder chart. The black, horizontal line represents an initial balance of the heart meter at a dial reading of 50 (corresponding to 10 cycles per second). Each departure of 5 small units of the heart record from this line represents a change of 1 cycle per second in "resultant" frequency, as explained previously under the discussion of filters.

The records of Fig. 14 are comparable to the ventricular volume records obtained by Wiggers and Katz,⁷ not only in general confirmation and timing in relationship to the cardiac cycle, but also in the relative size and shape when, with change in posture, there is a reduction of venous pressure and increase of heart rate.^{7, Figs. 7 and 11}

The interesting possibility that a direct measurement of cardiac output might be made from these records of cardiac vibration remains for future study.

More frequently the differential heart sound meter has been used with a simple needle galvanometer and the dial readings at balance recorded by the operator. In this way the average of a succession of heart beats is studied during a control period and after tilting, or a Master 2-step test. In both cases, after the subject has been supine, or seated, for five minutes, control readings are taken. He is then tilted, or performs the Master 2-step test. Readings are taken immediately after tilting and at thirty-second intervals for three to five minutes. In the exercise test, the subject sits immediately after the scheduled number of steps have been taken and readings of the meter dial are started at once and repeated every thirty seconds for five minutes.

The responses noted in a large number of Master 2-step exercise tests can be classed in four general types as shown in Fig. 15. The characteristics of these types are:

- (1) An increase of 5 to 15 dial units immediately after exercise with a return in less than 1.5 minutes to within 5 units of the control.
- (2) A rise of more than 15 units. Return in 1.5 minutes or delayed return.
- (3) A change of less than ± 5 units from control dial reading.
- (4) A fall of more than 5 units immediately after exercise. Intermediate types can exist.

For each type, the resting (control) reading may be at any point on the dial, but at present we consider the range of 40 to 55 as "normal." It is possible that further experience will narrow this range.

A high resting reading or a rise of more than 15 units immediately after exercise we interpret as a "stimulation." This stimulation occurs in the early stages of infection, or after inhalation of low concentrations of toxic chemicals. Failure to give an increased dial reading immediately after exercise we consider a "depression" reaction, indicating circulatory inadequacy. This is a frequent finding in fatigued workers or those acutely exposed to toxic chemicals.

A low resting dial reading appears to us the most important sign of inadequacy of the cardiovascular system. Physiologically, it will result from

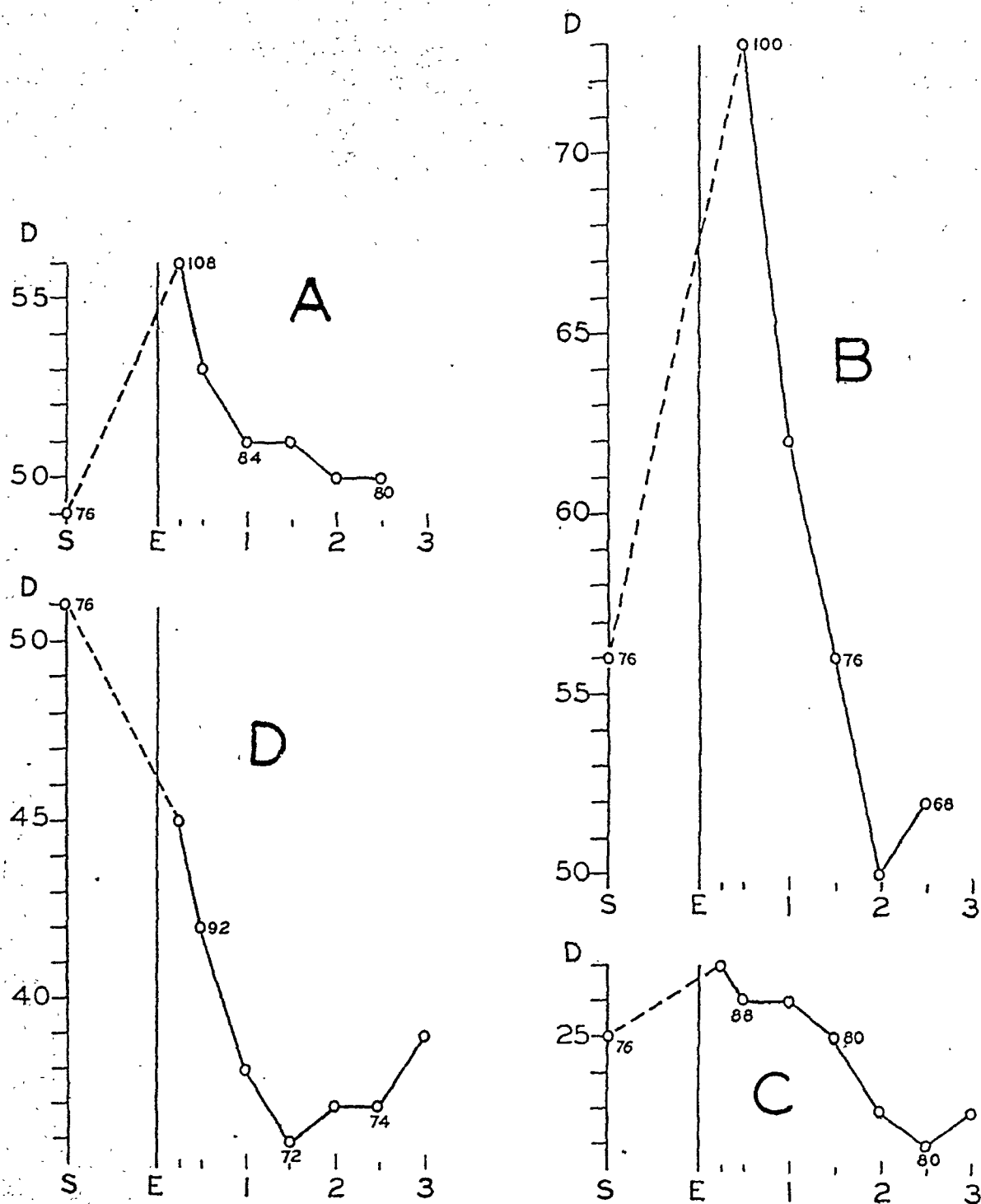


Fig. 15.—Types of response to Master 2-step test shown by differential heart sound meter: *D* = meter dial reading; *S* = reading after 5 minutes sitting; and *E* = end of exercise. Base line = minutes. Small numerals beside each circle indicate pulse rate.

low tonicity of the heart muscle and may involve the low frequency vibrations Kountz and Wright² record as present in diseased and dying hearts.

For convenience in assessing the dial readings of the meter in the exercise test, we have drawn up an arbitrary system of scoring (Table V), which covers the possible variations in resting reading, degree of response, time of maximum response, and recovery. Each factor is given an index and a score. A record can be classified by either indices or total score.

Dial readings obtained from the heart sound meter using the Master 2-step exercise test can be coded according to (a) resting reading, (b) maximum response to exercise, (c) time after exercise at which maximum response is reached, and (d) time after exercise at which reading has returned to approximately resting value.

Within these four categories, records can be given indices and scores as shown in Table V.

TABLE V. CODE FOR ANALYSIS OF HEART SOUND METER

	INDEX	SCORE
A. Resting dial reading		
40-55	1	0
Above 55	2	10
Less than 40	3	60
Less than 30	4	80
B. Maximum response to exercise		
Rise of 5 to 15 points	1	0
Rise of more than 15 points	2	4
Change (rise or fall) of less than 5 points	3	20
Fall of 5 or more points	4	40
C. Time of first maximum response to exercise		
Maximum change (rise or fall) observed		
0 to 0.5 minute	1	0
Above 0.5 but not above 1 minute	2	1
Above 1 minute but not above 1.5 minutes	3	1
Above 1.5 minutes	4	4
D. Rate of first return, after exercise, to within 5 points of resting reading		
0 to 0.5 minute	1	0
Above 0.5 but not above 1.5 minutes	2	0
Above 1.5 but not above 2 minutes	3	5
Above 2 minutes	4	5
(also in case of maximum response under Index B-3 above)		

Heart sound records scored as above can be classified according to the total score obtained by adding scores under A, B, C, and D.

It must be emphasized that the heart sound meter primarily discloses *functional* changes in heart vibration frequencies in response to physiologic loads. Function may be unimpaired even in a circulatory system which is manifestly diseased, as long as that system is adequately compensated. On the other hand, function may depart from normal when disease is not manifest. However, the most important question for a patient with cardiovascular disease is, "How great a physiologic load can I stand without failure of cardiovascular function?" To show how the differential heart sound meter may help to answer this question, we list in Table VI the results of its application, with the Master 2-step test, to a series of patients presented for special examinations of the cardiovascular system. The majority was tested only once. Most were of middle age. The tests are grouped according to score, and pertinent data from the medical record (often extending over years) are entered.

TABLE VI. RESULTS OF APPLICATION OF HEART SOUND METER AND SCORING CODE TO THIRTY-SEVEN CASES

CASE	SEX	AGE	DATE	INDEX				TOTAL SCORE	MEDICAL RECORD
				A	B	C	D		
1	M	41	?	1	1	1	1	0	Apparently normal
2	M	43	5/14/45	1	1	1	1	0	Apparently normal
3	M	58	9/12/45	1	1	1	1	0	No definite diagnosis. ECG on 9/11/45 suggested "intraventricular block"
4	M	54	4/23/45	1	1	1	1	0	Coronary thrombosis—2 attacks. (See records with high score below*)
5	M	56	8/31/45	1	1	1	1	0	No clinical diagnosis. 9/7/45 record suggested "angina of effort"
6	M	53	3/12/46	1	1	1	3	6	Hypertension
7	M	46	2/ 6/45	1	3	1	1	20	1917: Thyroidectomy
8	M	56	8/14/45	1	3	2	2	21	1937: Duodenal ulcer
9	M	41	1/25/45	1	3	1	1	20	Neurocirculatory asthenia
†10	M	40	2/ 2/45	1	3	1	1	20	Mild hypercholesterinemia—anginal pains
11	M	44	9/ 4/45	1	3	1	1	20	Mild, indefinite chest pains. (See record below with higher score†)
12	M	35	8/29/45	1	3	1	1	20	Precordial and substernal pain. Pain in left arm
13	M	51	9/20/45	1	3	1	5	26	Paroxysmal auricular tachycardia
14	M	42	4/29/46	1	3	4	4	29	Diastolic hypertension
15	M	36	8/ 1/45	1	4	1	1	40	Coronary occlusion
16	M	52	1/23/45	1	4	1	2	40	(?) 1944
10	M	40	4/ 4/45	1	4	1	4	45	ECG—"Posterior type myocardial infarction"
17	M	54	8/24/45	1	4	4	3	49	B.P. 94/64-60. See record 2/2/45
18	M	58	12/10/45	1	4	3	4	46	Hypertensive cardiovascular disease. Evidence of myocardial insufficiency
19	M	52	4/ 9/45	1	4	1	1	40	9/4/45: ECG—"Possible chronic coronary insufficiency"
20	F	28	1/17/45	4	1	2	4	86	Anginoid pains
21	M	60	3/ 8/46	3	1	1	4	65	Poor posture. Underweight
22	M	31	5/ 3/45	4	1	1	1	80	Cardiac episode 12 years ago
23	M	59	9/19/45	3	4	1	1	100	No clinical diagnosis
24	M	37	2/ 5/45	3	1	1	1	60	1939 ECG—left axis deviation.
25	M	34	9/26/45	3	3	1	1	80	"Suggests some myocardial abnormality, possibly due to age"
26	M	35	12/17/45	4	3	4	4	109	Rheumatic heart disease
27	M	46	4/10/45	3	3	1	1	80	Paroxysmal tachycardia. B.P. 150/90-88
28	M	56	9/24/45	3	1	1	1	60	Abnormal ECG. Fluoroscope "suggests mitral disease"
29	M	35	9/ 5/45	3	1	1	1	60	Diastolic hypertension
30	M	45	1/24/46	3	1	1	1	60	Apparently normal
*4	M	54	4/27/45	3	1	1	4	65	"Nervous exhaustion"
*4	M	54	4/30/45	3	1	1	1	60	Nitroglycerin poisoning
31	M	29	5/23/46	3	1	1	4	65	{ Coronary thrombosis—2 attacks (See record with lower score above)
									Bradycardia (excessive vagal activity)

TABLE VI. RESULTS OF APPLICATION OF HEART SOUND METER AND SCORING CODE TO THIRTY-SEVEN CASES—(CONT'D)

CASE	SEX	AGE	DATE	INDEX				TOTAL SCORE	MEDICAL RECORD
				A	B	C	D		
32	F	32	2/ 2/45	3	1	3	1	60	Exophthalmic goiter
33	M	71	4/28/45	3	1	1	4	65	Acute coronary occlusion—1937
34	M	46	9/13/45	3	3	2	2	81	Repeated ECG with low amplitude T waves
35	M	43	3/21/45	3	1	1	1	60	4/11/45: Anginoid pains
36	M	59	12/10/45	4	1	1	1	80	History of coronary insufficiency. 12/10/45: ECG—"Coronary disease—posterior type infarction"
37	F	24	1/24/45	3	3	1	1	80	Low systolic and diastolic blood pressure

In Table VII, the data are regrouped according to age and score.

The possible variations in functional efficiency even in the presence of disease are shown by Patient 4, who has had at least two severe coronary episodes. His record shows:

DAY	DATE	HEART SOUND RECORD				
		INDEX				TOTAL SCORE
Monday	4/23/45	1	1	1	1	0
Friday	4/27/45	3	1	1	4	65
Monday	4/30/45	3	1	1	1	60

On Monday, 4/23/45, his resting dial reading and his response to the Master 2-step Test were "normal." A week of work produced a drastic change. On Friday, his resting value was low and although the rise immediately after exercise was at least 5 points, the absolute value of the dial was still below 40. On this day, he failed to return to within 5 points of resting in one and one-half minutes. A weekend of "rest" produced little change: merely a more rapid return to resting value after exercise. The possible value of the meter in deciding ability to withstand a given physiologic load is here demonstrated.

The response of the differential heart sound meter to the tilt test follows the same general types as that to the exercise test. But a given subject may not show identical responses to the two tests at a particular examination. Fig. 16 shows data on three subjects. *A* responded normally in both tests. *B* failed to show a rise of dial reading in the tilt test, but was normal in the exercise test. *C* showed a fall from the control in both tests. Subject *B*'s behavior at the time of examination is similar to that of troops standing rigidly at attention for long periods. In some, a fall of muscle tonus leads to failure of venous return and syncope. Shuffling of the feet or occasional movement will restore adequate cardiac function.

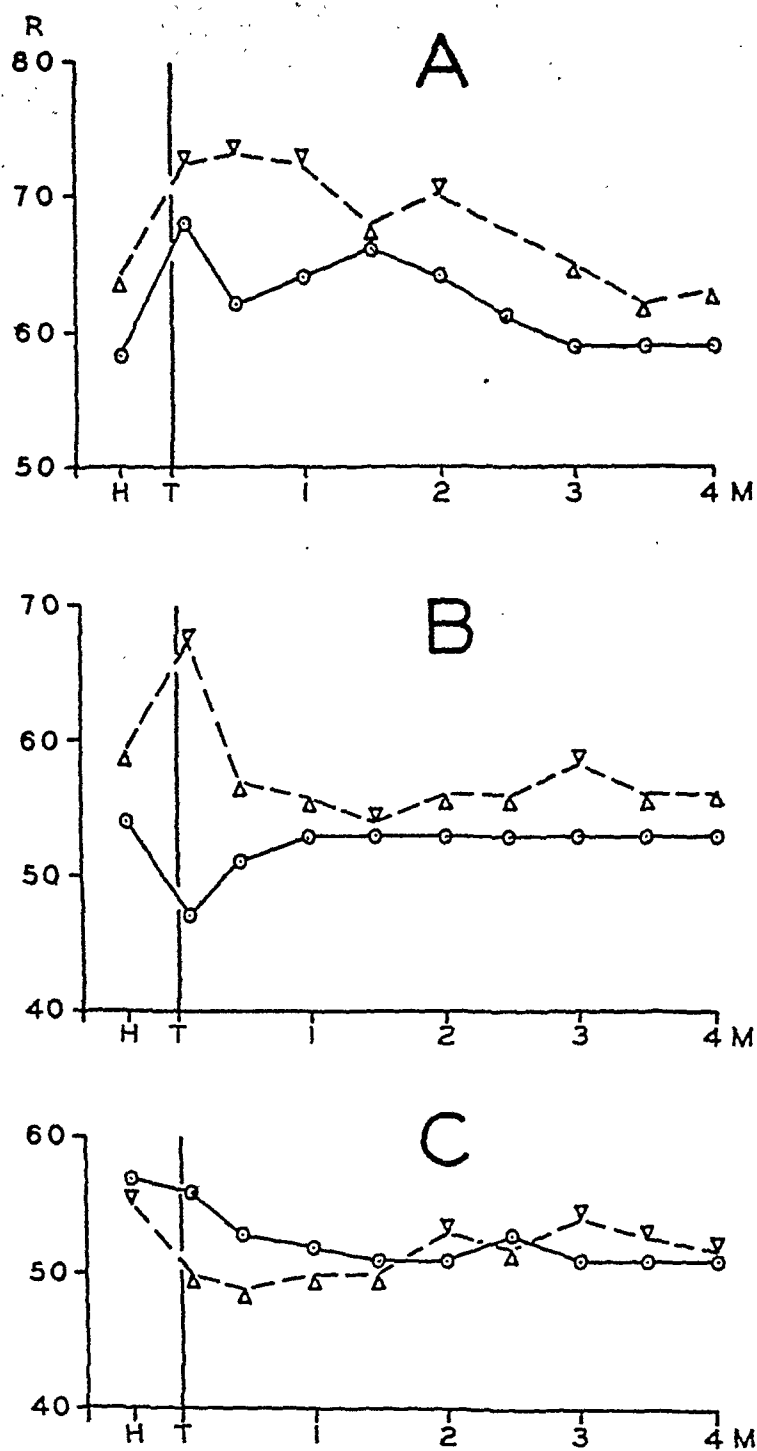


Fig. 16.—Comparison of results of tilt test (circles—full line) and Master 2-step test (triangles, broken line) in three subjects.

TABLE VII. DISTRIBUTION OF THIRTY-SEVEN CLINICAL CASES BY AGE AND HEART SOUND METER SCORE

AGE GROUP	SCORE			
	0-1	4-39	40-59	ABOVE 59
		GOOD RESTING VALUE	POOR EXERCISE RESPONSE	POOR RESTING VALUE
	MEDICAL RECORD			
20-29				Poor posture—underweight. Low blood pressure. Bradycardia (excessive vagal activity)
30-39		Paroxysmal auricular tachycardia	Coronary occlusion and hypertension	No diagnosis. Paroxysmal tachycardia. Rheumatic heart disease. Nervous exhaustion. Exophthalmic goiter
40-49	Normal Normal	Thyroidectomy and duodenal ulcer. Anginal pains—high blood cholesterol. Precordial and substernal pain. Coronary occlusion—1940	Low blood pressure	Diastolic hypertension. Nitroglycerin poisoning. Low amplitude T waves in ECG. Anginal pains
50-59	(?) Intraventricular block. Old coronary thrombosis.* Effort angina	Hypertension. Neurocirculatory asthenia. Diastolic hypertension	Posterior myocardial infarction. Hypertensive heart disease. Chronic coronary insufficiency. Anginal pains	Myocardial abnormality (geriatric). No diagnosis. Coronary thrombosis.* Coronary disease; posterior infarct. Old cardiac patient
60+				Acute coronary occlusion—1937

*Case 4, which, as described in the text, appears in both low and high score groups.

SUMMARY

1. Low frequency (0 to 20 cycles per second) vibrations are present in the heart vibration spectrum in both health and disease, and can be picked up at the chest wall by suitable apparatus.

2. The contribution of individual frequencies to the total intensity varies in rhythmic fashion during each separate heart beat and, under influence of the respiratory cycle, from beat to beat.

3. Physiologic stress, such as change of posture, graded exercise, or exposure to toxic chemicals, changes the distribution of intensity among frequencies, and the degree and direction of change can be an index of the ability of the cardiovascular system to respond to stress.

4. The change of distribution of intensity of vibration over frequencies during the heart beat may be related to the rate of change of ventricular volume and is affected by those physiologic factors which control the speed and extent of ventricular volume change.

5. Suitable apparatus has been devised to demonstrate these changes in a manner applicable to frequent routine study of human subjects, well or ill.

REFERENCES

1. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, *AM. HEART J.* 23:591, 1942.
2. Kountz, W. B., and Wright, S. T.: Comparison of Total Vibrations Obtained From a Normal, Rapidly Dying, Human Heart With Those Obtained in Chronic Myocardial Disease, *AM. HEART J.* 27:396, 1944.
3. Stumpff, Karl: *Grundlagen und Methoden der Periodenforschung*, Ann Arbor, 1937, J. W. Edwards. (By authority of the Alien Property Custodian.)
4. Stumpff, Karl: *Tafeln und Aufgaben zur Harmonischen Analyse und Periodogrammrechnung*, Ann Arbor, 1944, J. W. Edwards. (By authority of the Alien Property Custodian.)
5. Master, A. M.: The Electrocardiogram After Exercise: A Standard Heart Function Test, *U. S. Nav. M. Bull.* 40:346, 1942.
6. Henderson, Y., and Haggard, H. W.: *Noxious Gases*, ed. 2, New York, 1943, Reinhold Publishing Corporation, pp. 167 and 168.
7. Wiggers, C. J., and Katz, L. N.: The Contour of the Ventricular Volume Curves Under Different Conditions, *Am. J. Physiol.* 58:439, 1922.
8. Lamb, H.: *The Dynamical Theory of Sound*, ed. 2, London, 1931, Edwin Arnold & Co., pp. 74 and 75.

COMPLETE HEART BLOCK IN YOUNGER AGE GROUPS

J. HAMILTON CRAWFORD, M.D., AND N. J. DI GREGORIO, M.D.*

BROOKLYN, N. Y.

COMPLETE heart block is one of the least common disturbances of the cardiac mechanism. When accompanied, as it frequently is, by the Adams-Stokes syndrome it is one of the most dramatic. White¹ states that at the Massachusetts General Hospital, in a series of 10,000 cases, the incidence of complete heart block was 0.79 per cent. By far the largest number of cases occur in older age groups and are a result of coronary artery disease. In seventy-two cases of complete A-V block, Grabel and White² found the distribution to be: coronary disease, 47; congenital heart disease, 4; possible congenital heart disease, 2; rheumatic fever, 3; cardiovascular syphilis, 3; possible diphtheria (history of early infection), 4; and unknown, 9. In view of the fact that coronary disease preponderates to such an extent as the etiological agent and the prognosis is poor when this is the causative factor, it seemed to us worth while to study cases below the age of forty years when coronary disease is not prevalent. Complete heart block below the age of forty may be due to (1) congenital heart disease, (2) rheumatic heart disease, (3) diphtheria, (4) acute general infections, sometimes with abscess formation involving the bundle, (5) syphilis, acquired or congenital, (6) ulcerative endocarditis, (7) trauma, (8) diffuse fibrosis of the myocardium due to arteriosclerosis of the coronary arteries or of unknown etiology, (9) tumor of the heart, congenital or acquired, (10) digitalis, and (11) undetermined etiological causes.

Complete heart block due to congenital heart disease is not common but is well recognized. The desirable criteria for such a diagnosis are (a) proof by graphic methods, (b) a slow pulse at an early age, (c) signs of congenital heart disease, (d) the absence of a history of infection which might be a possible cause of the block; rheumatic fever, and diphtheria, for example. Yater³ analyzed all the reported cases of congenital heart block in 1929 and found only thirty cases which fulfilled the necessary criteria. In 1929, Yater, Lyon, and McNabb⁴ again analyzed the cases and found forty-four acceptable cases of which thirty-five showed complete heart block. In 1934, Yater, Leamann, and Cornell⁵ accepted six more cases from the literature and reported another. It is unnecessary to review these cases as they have been fully discussed by Yater and his colleagues. Campbell and Suzman⁶ reported eight cases in 1934. Currie⁷ described one case in 1940; Perez de los Reyes and associates⁸ added four cases in 1943, and recently,

Received for publication Nov. 25, 1946.

*From the Kings County and Long Island College Hospitals, and the Long Island College of Medicine.

Waldman⁹ has added another, in which paroxysms of complete heart block took place in a young individual with a patent ductus arteriosus. In all, approximately fifty patients have been described in whom complete heart block appeared to be of congenital origin. It is probable that more exist, since in many instances the condition is asymptomatic and is not associated with such outstanding signs as dyspnea, cyanosis, and clubbing of the extremities. As a rule, in congenital complete heart block the idioventricular rate is faster than is common in older age groups; hence, the condition may not be suspected. Campbell and Suzman state that the rate may vary from 42 to 56 beats per minute. Again, heart block in an older individual may have existed since childhood before being recognized and may then be attributed to coronary artery disease, which would be the usual etiological agent at that time.

The commonest form of congenital heart disease to be associated with complete heart block is an interventricular septal defect. Complete block is, however, rare even when this is present. Sprague and White¹⁰ state that complete heart block, even as a transient phenomenon, is rare in rheumatic fever and our experience conforms to this statement. The common lesion in rheumatic fever is a transient partial block. Campbell and Suzman saw only two cases of complete heart block due to rheumatic fever. Sprague and White express the view that antecedent diphtheria remains to be proven as a cause of complete heart block in younger individuals. In this disease, although temporary partial heart block is common, the occurrence of complete heart block is associated with very severe illness and an extremely bad prognosis so that these individuals are unlikely to survive. White and Jones¹¹ analyzed 100 patients who had suffered from diphtheria and found no instance of persistent heart block. Alstead¹² in a similar study found only one case. Rosenberg¹³ reported two cases of transient complete heart block in mumps, and Paul, Rhomberg, and Cole¹⁴ reported two similar cases in scarlet fever.

Generalized infections may produce temporary partial block, but complete block, either temporary or permanent, is very uncommon. It would be more likely to follow pyogenic infections with abscess formation involving the course of the bundle of His.

Syphilis, either congenital or acquired, is a very rare cause. In this disease the most likely cause would be gummata involving the bundle of His.

Ulcerative endocarditis with ulceration through the septum involving the bundle is another unusual cause. We know of a case of subacute bacterial endocarditis due to *Streptococcus viridans* in which a patient developed complete heart block which autopsy proved to have been the result of ulceration through the septum, resulting in severance of the main bundle.

Trauma is always a doubtful factor in the causation of cardiac lesions unless the effects can be proven to follow immediately after the episode has taken place. Sprague and White state that they have seen two individuals with complete heart block in whom trauma might have been the etiological agent.

Arteriosclerosis of the coronary arteries can occur in young individuals and coronary occlusion may take place. When the vessels which supply the bundle of His are seriously involved complete heart block may be present. The bundle

may also be involved by a diffuse fibrotic process for which no etiological cause can be determined.

Obviously, digitalis must be ruled out as a factor in any case which has been receiving this drug.

Finally, there are some cases in which, even after autopsy examination, no definite causative factor can be determined.

Sprague and White reported a series of young individuals in whom complete heart block was present. Infectious disease (in three), rheumatic fever (in two), congenital heart disease (in one), trauma (in one) were the probable etiological agents, while in four they were unable to determine the cause. Leamann¹⁵ reviewed the literature in 1933 and found approximately 100 cases in the younger age groups of which forty-two were congenital. He reported one case and stated that Ashman had seen another.

The fourteen cases which will be presented represent the examples of complete heart block seen in individuals below the age of forty years in hospitals and private practice over a period of about ten years. In view of the large number of admissions of patients suffering from cardiovascular lesions the rarity of the condition is apparent. Two cases were of congenital origin, and three others were probably congenital, although the evidence was not conclusive, six, in two of which the complete heart block was temporary, were due to rheumatic infections, two were caused by arteriosclerosis, and in one no satisfactory explanation of the lesion was found even after autopsy.

CASE REPORTS

CASE 1.—E. S., a white girl 15 years of age, was admitted to Kings County Hospital on Jan. 25, 1940. The patient had been found to have heart disease at the age of 7 years, and since that time attended a cardiac class at school. One week before admission she developed sore throat and temperature, which persisted. On the day of admission vomiting was present and the temperature was 104.6° Fahrenheit. The pulse rate was 100, and respirations were 26 per minute. The blood pressure was 106/56. There were questionable petechiae in the mouth. The entire precordium bulged. An x-ray film of the chest showed a globular configuration of the heart. A thrill was present over the pulmonary area. A loud machinery-like murmur was heard over the pulmonary area. Bigeminal rhythm was present. Bilateral basal râles were heard in the lungs. The spleen was palpable. Patient was placed on sulphapyridine. The white blood count fell to 2,200 on January 29, but gradually rose again. Two blood cultures were negative. The Wassermann was negative. An electrocardiogram taken on January 21 showed complete heart block with an auricular rate of 125 and a ventricular rate of 80 beats per minute. It was otherwise normal. Another tracing taken on February 2 was identical. On Feb. 6, 1940, the patient suddenly expired in bed, although she had been showing slow improvement up to this time.

CASE 2.—M. L., a white boy, 12 years of age, was admitted to Kings County Hospital on July 13, 1937, complaining of pain in the right ear of four days' duration. There were no symptoms referable to the cardiovascular system. Right-sided otitis media was present. The temperature was 100°F. and the pulse rate was 60 per minute. An x-ray film of the heart showed marked prominence in the region of the pulmonary conus, compatible with a diagnosis of some type of congenital heart disease. There was a harsh systolic murmur heard widely over the precordium, but loudest at the apex. The physical examination offered no other important findings. The blood Wassermann test was negative. An electrocardiogram, taken on July 15, showed complete heart block with an auricular rate of 60 and a ventricular rate of 40 per minute. It was otherwise normal. He was discharged on July 21, 1937.

CASE 3.—N. L. B., a Negro woman 23 years of age, entered the prenatal clinic of Kings County Hospital on Sept. 30, 1941, at which time she was five months pregnant. During routine examination the pulse rate was found to be 62 per minute. The blood pressure was 130/80. There was a systolic murmur at the level of the fourth left costal cartilage and also at the apex. She was referred to the cardiac clinic for further study. She stated that she had always been well and had never suffered from rheumatic fever, chorea, diphtheria, or scarlet fever. X-ray examination showed slight cardiac enlargement. Except for the findings mentioned, the physical examination was negative. The blood Wassermann test was negative. An electrocardiogram showed complete heart block, with an auricular rate of 100 and a ventricular rate of 62 per minute. It was otherwise negative. On November 29, she was delivered without difficulty and had a normal post-partum course. An electrocardiogram, taken just before delivery, and another after delivery, were exactly the same as the first. The patient did not continue to attend the cardiac clinic with regularity. She reappeared on Feb. 8, 1943, again five months pregnant. The physical condition was unchanged. The electrocardiogram, at this time, was the same as the previous records. There was no difficulty during this pregnancy and she was delivered uneventfully on June 27, 1943. She again failed to attend the clinic.

CASE 4.—N. M., a 23-year-old white woman, was first seen on March 5, 1943. Her only complaint was that of fatigue. Otherwise, she had always felt well and had been active in athletics. She had suffered from pneumonia and empyema at the age of 8 years. There was no history of rheumatic fever, chorea, or joint pain. Physical examination revealed a pale, rather underweight, young woman. The pulse rate was 56 per minute. The blood pressure was 126/80. X-ray examination showed slight left auricular enlargement but no evidence of left ventricular enlargement. There was a systolic murmur heard over the entire precordium. The murmur was best heard in the recumbent position. An electrocardiogram showed complete heart block, with an auricular rate of 80 and a ventricular rate of 56 per minute. It was otherwise negative. The remainder of the physical examination was unimportant. Shortly after this, the patient had an uneventful pregnancy and was delivered without difficulty on March 31, 1944. She was pregnant again, in 1946, and had no symptoms.

CASE 5.—F. T., a 27-year-old white woman, was admitted to Kings County Hospital on June 12, 1939. At the age of 6 years, the patient had had spinal meningitis. Since then she has had a speech defect and has been markedly ataxic. She sought advice because of frequent attacks of urticaria. The pulse had been known to vary from 36 to 38 beats per minute since childhood. The neurological diagnosis was bilateral cerebellar disease following encephalitis in childhood. The heart rate was 40 beats per minute. X-ray examination of the heart showed slight left ventricular enlargement. There was a harsh systolic murmur at the apex. The rest of the physical examination was unimportant. The blood Wassermann test was negative. An electrocardiogram, taken on June 18, showed auricular fibrillation and complete heart block with a ventricular rate of 40 per minute. The tracing was otherwise negative. Patient was discharged on June 21, 1939.

CASE 6.—J. B., a white boy 12 years of age, was admitted to Kings County Hospital on March 3, 1941, complaining of vague abdominal pain and vomiting. He had had a recent attack of sore throat. The previous history was negative for rheumatic fever, chorea, and joint pain. Tonsillectomy had been performed at the age of 6 years, but, nevertheless, he had had an occasional sore throat. At the time of the tonsillectomy, he was told at another hospital that he had a weak heart. Physical examination revealed pharyngeal injection and vague abdominal tenderness. The temperature was normal but he had a slight leucocytosis. The heart rate varied between 43 and 60 beats per minute. X-ray examination revealed slight generalized enlargement of the heart with a mitral configuration and some left auricular enlargement. There were presystolic and systolic murmurs at the apex. The rest of the physical examination was negative. The sedimentation rate was slightly elevated at the beginning but soon returned to normal. The circulation taken on March 5 showed complete heart block with an auricular rate of 88 and a ventricular rate of 46 per minute. The tracing was otherwise normal. Another tracing taken on March 18 showed an auricular rate of 72 and a ventricular rate of 43 per minute. He was discharged on

March 28, 1941. He was seen in the cardiac clinic on Aug. 25, 1941, at which time he had no complaints. An electrocardiogram, at this time, showed complete heart block with an auricular rate of 88 and a ventricular rate of 45 per minute. It was otherwise normal.

CASE 7.—E. B., a 25-year-old colored woman, was admitted to Kings County Hospital on July 8, 1941, complaining of pain and tenderness in the right buttock. An abscess was incised and drained with complete cure. Patient had had an ischiorectal abscess treated two years before and a recurrence a year and one-half later. There were no cardiovascular symptoms. Examination revealed a heart rate of 56 beats per minute. On x-ray examination the heart appeared normal. Physical examination revealed systolic and diastolic murmurs at the apex. The physical examination was otherwise negative, except for the abscess in the buttock. The blood Wassermann test was negative. An electrocardiogram, taken on July 14, 1941, showed complete heart block with an auricular rate of 75 and a ventricular rate of 56 per minute. It was otherwise normal.

CASE 8.—W. T., a white man 39 years of age, was admitted to Kings County Hospital on July 31, 1942. He complained of pain in the chest, of sudden onset. He had had rheumatic fever as a child and was known to have rheumatic heart disease. Dyspnea and ankle edema had existed for two years. On admission the patient was coughing up bright red blood and the chest pain was aggravated by respiration. Physical examination revealed temperature of 100.6°F., a pulse rate of 120 beats per minute, and a blood pressure of 120/80. X-ray examination of the heart showed generalized enlargement. On auscultation a gallop rhythm was present and presystolic and diastolic murmurs were heard at the apex. The lungs showed evidence of consolidation at the right base, which was confirmed by x-ray films. The liver was moderately enlarged, and there was pitting edema of the extremities. The blood Wassermann test was negative. Blood chemistry studies were normal. There was a trace of albumin in the urine. Electrocardiograms, taken on September 3 and 21, and again on October 14, showed first stage heart block (P-R 0.24) and other changes which were interpreted as evidence of myocardial damage. On September 11, complete heart block was present with an auricular rate of 75 and a ventricular rate of 60 per minute. The patient improved and was discharged on Nov. 27, 1942.

CASE 9.—J. K., a 23-year-old white man, was admitted to Kings County Hospital on July 7, 1938. He had had rheumatic fever at the age of 15 years. Two years later he was told that he suffered from heart disease. At the age of 22, the left leg was amputated at the knee for osteomyelitis. On admission, he complained of cough and temperature of one week's duration. The temperature was 101°F. and the pulse rate was 80 per minute. The systolic blood pressure was 140; the diastolic pressure could not be accurately determined since the sounds could be heard to zero. There was clubbing of the fingers. X-ray films of the heart showed cardiac enlargement. There was a presystolic murmur at the apex, followed by a snapping first sound. Systolic and diastolic murmurs were heard at the aortic area. Patient had consolidation at the base of the left lung and fluid in the pleural cavity. The blood examination showed a white cell count of 13,200 and a hemoglobin of 78 per cent. The latter rapidly fell to 38 per cent, while the white cell count showed little change. Blood cultures were negative. The blood Wassermann test was negative. The urine was normal. Electrocardiograms, taken on July 24 and August 27, showed sinus tachycardia with rates of 115 and 120 beats per minute, respectively. They were otherwise normal. Another, taken on October 3, revealed complete heart block with an auricular rate of 107 and a ventricular rate of 70 beats per minute. Evidence of myocardial damage was also present. Patient's condition progressively deteriorated and he died on Oct. 9, 1938.

CASE 10.—P. C., a 12-year-old white girl, was admitted to Kings County Hospital on April 7, 1938, suffering from cough of two weeks' duration, sore throat, and pain in the right ear. Ten days before, she had had pain in the left knee. The family physician stated that she had heart disease. On examination, the heart rate was found to be 40 per minute. The systolic blood pressure was 84; the diastolic pressure could not be accurately determined since the sounds were heard to zero. X-ray films of the heart revealed a globular configuration with enlargement of the left ventricle. There was a systolic murmur at the apex and also a mid-diastolic murmur in this

region. A diastolic murmur was heard along the left border of the sternum. An arterial pistol shot sound was heard and capillary pulsation was present. The physical examination was otherwise negative. The urine was negative, as was the blood Wassermann test. The hemoglobin was 70 per cent and the white blood count was 9,500. An electrocardiogram, taken on April 8, showed complete heart block with an auricular rate of 110 and a ventricular rate of 40 per minute. It was otherwise normal. Another, taken on May 12, had an auricular rate of 125 and a ventricular rate of 40 per minute. The patient was discharged on July 15, 1938.

CASE 11.—C. S., a Negro woman 29 years of age, was admitted to Kings County Hospital on Jan. 23, 1940. She had had rheumatic fever in 1939 and her joints had been rather painful ever since, but she had been able to attend to her usual duties. She had had tonsillitis several weeks before admission. She complained of pain in the precordial area on breathing, palpitation, and dyspnea. The temperature was 103°F. and the pulse rate was 124 per minute. The blood pressure was 122/90. The throat was congested. X-ray films of the heart showed some cardiac enlargement and a mitral configuration with enlargement of the left auricle. There was a loud systolic murmur at the apex. The physical examination was otherwise unimportant. The sedimentation rate was elevated at the beginning of our observations but soon returned to normal. The blood Wassermann test was negative, as was a gonococcal fixation test. An electrocardiogram, taken on January 25, showed complete heart block with an auricular rate of 100 and a ventricular rate of 81 beats per minute. The T waves were negative in Leads II and III. Another electrocardiogram, taken on February 7, was normal. The rate was 67 per minute and the T waves were now positive. The patient was discharged on Feb. 14, 1940.

CASE 12.—M. S., a 39-year-old Negro man, was admitted to Kings County Hospital on March 27, 1935, complaining of pain in the lower chest and dyspnea. These symptoms had been present for two years and he had been in a hospital one month before with similar complaints. He gave a history of syphilis for which he had received treatment. He stated that he had had rheumatic fever at the age of 20 years. On admission, the temperature was 103.2°F., the pulse, 120 per minute, and the blood pressure, 122/94. X-ray films of the heart showed elongation and widening of the aorta and cardiac enlargement. A systolic murmur was present at the apex and a gallop rhythm was heard. There were râles throughout the chest and edema of the legs developed. The blood Wassermann test was negative. An electrocardiogram, taken on April 3, showed complete heart block with an auricular rate of 100 and a ventricular rate of 50 per minute. There was also evidence of myocardial damage. The condition became gradually worse and he died on May 23, 1935.

Autopsy: The heart weighed 610 grams. The ventricles were dilated and hypertrophied. The valves were normal. The ventricular muscle was diffusely fibrotic. The aorta showed plaques which suggested syphilitic aortitis. There was a moderate amount of arteriosclerosis of the coronary arteries. The lungs showed passive congestion, as also did the liver, spleen, and kidneys.

CASE 13.—M. R., a 29-year-old white man, was admitted to Kings County Hospital on Jan. 14, 1943, complaining of severe precordial pain of sudden onset which radiated to both shoulders and down the left arm. There was no history of previous serious illness. On admission, the heart rate was 53 beats per minute and the blood pressure was 98/60. The temperature was 100.6° Fahrenheit. The physical examination of the heart showed no cardiac enlargement and no murmurs. The rest of the physical examination revealed no important findings. An electrocardiogram, taken on the day of admission, showed complete heart block, with an auricular rate of 125 and a ventricular rate of 53 per minute. Right bundle branch block was also present and the tracing, despite the bundle branch block, suggested acute infarction of the anterior wall of the left ventricle. Another, taken on January 20, showed sinus rhythm and persistence of the right bundle branch block. The patient had temperature for four days. He left the hospital, against advice, on Jan. 27, 1943.

CASE 14.—C. S., a 24-year-old white truckman, was admitted to Long Island College Hospital on May 15, 1944. One year before admission, he had an attack of unconsciousness. This lasted a few minutes and was followed by a pounding headache. He had a second attack syncopal-like

on the day of admission. He did not become unconscious during this attack, but had to sit down. After ten minutes, he was able to get up but his gait was staggering. There was no history of rheumatic fever, chorea, or joint pain. As a child he tired easily. In 1918, he was told at another hospital that he had a heart murmur and that he suffered from congenital syphilis. He received antisypilitic treatment for five years. Physical examination revealed a man in good condition. The heart rate was 40 beats per minute and the blood pressure, 130/65. There was some enlargement of the heart, both to right and left, and x-ray films suggested the possibility of syphilitic aortitis. A loud systolic murmur was heard in the third and fourth intercostal spaces close to the sternum and a blowing systolic murmur was heard at the apex. The physical examination was otherwise unimportant. Blood chemistry studies and urinalysis were normal. The Kline reaction was slightly positive. The circulation times, both with saccharin and ether, were normal. An electrocardiogram, taken on May 11, showed complete heart block with an auricular rate of 84 and a ventricular rate of 43 beats per minute. The QRS complexes were of low voltage. Another tracing, taken on May 15, showed an auricular rate of 84 and a ventricular rate of 34 per minute. The T waves in Lead I were diphasic. The patient was discharged on May 23, 1944.

Second Admission: After he left the hospital he had a slight spell in which he did not become unconscious. On Nov. 8, 1944, he was seized with an attack in which he did become unconscious; this was followed by motor aphasia and right hemiparesis. At the end of four hours he became normal except for a pounding headache. The physical findings were the same as on the previous admission. There was a leucocytosis of 14,100. The spinal fluid was normal and the blood Wassermann test was negative. The basal metabolic rate was -3 per cent. An electrocardiogram, taken on November 10, showed complete heart block, with an auricular rate of 75 and a ventricular rate of 42 beats per minute. There were negative T waves in Leads I and II. On November 17, at 7:15 P.M., while walking in the ward, he fell down unconscious. He had tonic contractions on the right side and the left side moved aimlessly. The heart rate at first was 42 and later rose to 52 beats per minute. After fifteen minutes, uncontrolled activity ceased and slight hemiparesis remained. He did not regain consciousness and at 8:45 P.M. on November 19, he developed clonic convulsions, with intervals of relaxation. He died on Nov. 20, 1944, at 1:15 A.M.

Autopsy: The heart weighed 400 grams. There was a small patent foramen ovale. The valves were normal and there was no thickening of the chordae tendineae. The papillary muscles and columnae carneae appeared normal. There was diffuse atheromatous degeneration of the aorta, most marked in the abdominal portion, and a moderate amount of atheroma of the coronary ostia. The lungs and abdominal organs were normal except that the left adrenal was fibrotic and contained yellowish-white calcified material. The right adrenal was normal. The thyroid was enlarged and contained a large amount of colloid; there were also a few small adenomata. The brain showed a thickened dura which was adherent to the brain tissue in places, especially over the left temporal area. On the basilar surface of the brain, near the junction of the frontal and temporal areas in the midline, there was a diffuse area of softening and necrosis. There was a thrombus in the left middle cerebral artery.

Microscopic examination of the heart revealed that the myocardium, except in the region of the septum, was normal. The endocardium was slightly thicker than normal. In the septum the endocardium was diffusely thickened and fibrous on both sides. From the thickened endocardium, fibrous strands extended into the myocardium of the septum. Small bundles of Purkinje fibres were enmeshed in the fibrous tissue. There was a small calcified area in the fibrous tissue. No serial sections were made.

DISCUSSION

The classification of these cases as to the cause which was responsible for inducing the complete heart block, when no autopsy is available, is obviously difficult in many instances. After autopsy it may still be impossible, even after careful microscopic study, to assign a cause as in Case 14. This patient had suffered from congenital syphilis but the pathologist did not consider the lesion

syphilitic. The evidence seemed reasonably clear that Case 1 suffered from a patent ductus arteriosus. Case 2 also seemed to be associated with a similar lesion although the evidence was less certain. In Cases 3 and 4 no cause could be found for the lesion unless the pneumonia and empyema from which Case 4 suffered at the age of 8 years might be the responsible factor in this instance. We know of no case where pneumonia and empyema have caused permanent complete heart block. There was slight left auricular enlargement in this case so that this disturbance may have been of rheumatic origin. There was no suspicion of rheumatic fever in Case 3. It is possible that a congenital lesion was responsible in both instances. Case 5 suffered from a severe neurological disorder as a result of spinal meningitis. Possibly this infection may have caused the heart block although, again, we know of no reported instance of this disease having induced complete block. In view of the history of a slow pulse since childhood, the heart block was probably of congenital origin. The evidence seems reasonably clear that rheumatic infection was responsible for the block in Cases 6 to 11. In Case 11, complete block was only temporary. Case 12 was found, at autopsy, to be due to coronary sclerosis. Obviously, in Case 13, who suffered from temporary complete heart block following coronary occlusion, the basic cause was arteriosclerosis, the bundle being involved in the zone of reaction surrounding the necrotic area. No etiological cause could be determined in Case 14 even after autopsy.

Pathology: Where permanent block is the result of either rheumatic fever, diphtheria, or pyogenic organisms, the mechanism of the block is fibrotic change in the bundle which prevents it from functioning properly. Similarly in trauma, there is presumably in the beginning a hemorrhage which is replaced by scar tissue. In Case 14 fibrous tissue interfered with conduction, although what caused this could not be determined. In syphilis the lesion which interrupts the bundle may be either an actual gumma or fibrous tissue. In tumor the malignant tissue destroys the fibers of the bundle, while in ulcerative endocarditis the bundle is severed by the ulcerative process. When the block is only temporary it may be due to marked cloudy swelling or to the involvement of the bundle by the zone of reaction surrounding an Aschoff body in rheumatic fever or the area of necrosis in coronary occlusion. In congenital heart disease with complete heart block Abbott¹⁶ states that only seven autopsies have been performed, and in only four of these has the bundle been studied by serial sections. Three of these were cases reported by Yater and colleagues, in which they found imperfect development of the bundle. The fourth was an instance of 2:1 block studied by Wilson and Grant¹⁷ in which they found that fibrous tissue had penetrated the bundle, thus damaging the fibers. The commonest pathologic lesion associated with congenital complete heart block is a patent interventricular septum. It must be noted, however, that complete heart block is rare in patent interventricular septum because, as a rule, the defect lies *anterior to the membranous part* of the septum while the bundle runs posterior to it. Alterations in tension in the bundle may be responsible when conduction is imperfect. Such a cause has been suggested, when the degree of conduction varied under different circumstances, by

congenital lesions and in cases which may have been due to diphtheria in early life. Likewise in trauma, if only the bundle is damaged, the prognosis is good. It is much worse in cases in which rheumatic fever or syphilis are the causative factors and is poor when coronary disease is the cause. When a tumor, an abscess, or an ulcerative process has severed the bundle the prognosis is usually extremely bad.

SUMMARY

1. Fourteen cases of complete heart block in individuals below the age of forty are described. Two of these were of congenital origin, six were due to rheumatic fever, two to arteriosclerosis, three were probably of congenital origin, although the evidence was not conclusive, and in one no cause could be determined even after autopsy.

2. The etiological factors, the clinical features, the pathology, and the physiologic adjustments in such cases are discussed.

We wish to thank the various physicians at Kings County and Long Island College Hospitals for permission to utilize their records.

REFERENCES

1. White, P. D.: *Heart Disease*, ed. 3, New York, 1944, The Macmillan Company, p. 925.
2. Grabiell, A., and White, P. D.: Complete Auriculo-ventricular Dissociation, *Am. J. M. Sc.* 192:334, 1936.
3. Yater, W. M.: Congenital Heart Block. Review of Literature; Report of a Case of Heterotaxy. The Electrocardiogram in Destrocardia, *Am. J. Dis. Child.* 38:113, 1929.
4. Yater, W. M., Lyon, J. A., and McNabb, P. E.: Congenital Heart Block. Review and Report of Second Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, *J. A. M. A.* 100:1831, 1933.
5. Yater, W. M., Leamann, W. G., and Cornell, V. H.: Congenital Heart Block. Report of the Third Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, *J. A. M. A.* 102:1660, 1934.
6. Campbell, M., and Suzman, S. S.: Congenital Complete Heart Block, *AM. HEART J.* 9:304, 1934.
7. Currie, G. M.: A Case of Congenital Complete Heart Block. The Effect of Atropine, *Brit. M. J.* 1:769, 1940.
8. Perez de los Reyes, R., de la Torre, H., Alvarez, A. D., and Costa, J.: Los Bloqueos Cardiacos en la Infancia, *Arch. de med. inf.* 12:9, 1943.
9. Waldman, S.: Transient Heart Block in Congenital Heart Disease, *AM. HEART J.* 30:92, 1945.
10. Sprague, H. B., and White, P. D.: High Grade Heart Block Under the Age of Thirty, *M. Clin. North America* 10:1235, 1927.
11. White, P. D., and Jones, T. D.: The Heart After Severe Diphtheria, *AM. HEART J.* 3:190, 1927.
12. Alstead, S.: The Electrocardiogram in Diphtheria, *Quart. J. Med.* 1:277, 1932.
13. Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis), *Arch. Int. Med.* 76:257, 1945.
14. Paul, W. D., Rhomberg, C., and Cole, J.: Transitory A-V Block Occurring During Scarlet Fever, *AM. HEART J.* 31:138, 1946.
15. Leamann, I. I.: Heart Block in the Young, *Tr. A. Am. Physicians* 48:195, 1933.
16. Abbott, M. E.: In Stroud, W. D.: *Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, 1940, F. A. Davis Company, p. 21.
17. Wilson, J. C., and Grant, R. T.: A Case of Congenital Malformation of the Heart in an Infant Associated With Partial Heart Block, *Heart* 12:295, 1926.

18. Nissé, B. S.: Congenital Malformation of the Heart Associated With Heart Block, *Proc. Roy. Soc. Med.* 21:438, 1927.
19. Smith, S. C.: High Grade Block, *J. A. M. A.* 76:17, 1921.
20. Calandre, L.: Tres Casos de Disociación Auricular-ventricular, *Arch. Cardiol. y Hemat.* 2:225, 1920.
21. Gessel, R.: Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve, *Am. J. Physiol.* 40:267, 1916.
22. Grollman, A.: Cardiac Output of Man in Health and Disease, Springfield, 1932, Charles C Thomas, Publisher.
23. Liljestrand, A., and Zander, E.: Studies of Work of Heart During Rest and Muscular Activity in Case of Uncomplicated Heart Block, *Acta. med. Scandinav.* 66:501, 1927.
24. Lunsgaard, C.: Untersuchungen über das Minuten Volumen des Hertzen bei Menschen. III, *Deutsches Arch. f. klin. Med.* 120:481, 1916.
25. Alt, H. L., Walker, G. L., and Smith, W. C.: Cardiac Output in Heart Disease, *Arch. Int. Med.* 45:958, 1930.
26. Stewart, H. J., Deitrick, J. E., Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms; Observations Relating to Rhythms Associated With Rapid Ventricular Rate and to Rhythms Associated With Slow Ventricular Rate, *J. Clin. Investigation* 17:449, 1938.
27. Jansen, J.: Heart Disease in Pregnancy, St. Louis, 1938, C. V. Mosby Company, p. 115.
28. Diddle, A. W.: Auriculo-ventricular Block in Pregnancy, *West. J. Surg.* 49:220, 1941.
29. Mitchell, F. X., Fettes, D. S., and Hollander, A. G.: Complete Heart Block Complicating Pregnancy, *Am. J. Obst. & Gynec.* 45:340, 1943.

THE HEART SIZE IN NEUROCIRCULATORY ASTHENIA, EFFORT SYNDROME, OR ANXIETY NEUROSIS

JACQUES CARLOTTI, M.D., MANDEL E. COHEN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

IN THE course of a completed investigation¹ of a series of patients, mostly soldiers, with neurocirculatory asthenia, anxiety neurosis, or effort syndrome, during the years 1942 to 1945 inclusive, the size of the heart was studied by tele-roentgenogram and the results are herein recorded.

In the past there have been several reports of investigation of heart size in neurocirculatory asthenia or effort syndrome in the majority of which emphasis has been placed on the apparently small size of the heart shadows. However, the selection of cases has not always been on the basis of the symptom complex and, therefore, on occasion the studies have been concentrated on, or even limited to, slender individuals with a tendency to vertical heart position.

Meakins and Gunson² in 1917 studied fifty patients with this condition orthodiagraphically. They found the average transverse diameter to be 12.8 cm. in contrast to the normal given in Dietlen's tables of 13.4 centimeters. In 1920³ they wrote that the transverse diameter of "the heart in cases of so-called irritable heart is on the average somewhat smaller (0.7 cm.) than normal."

Bernard Smith⁴ in 1920 studied 119 cases of effort syndrome in which measurements of the heart of men were made in the standing position with the target six and one-half feet from the plate. He stated in his summary that "cases of effort syndrome in which symptoms have persisted for a long time, have smaller hearts than normal when compared by measurements of transverse diameter, area, and volume Patients who acquired the effort syndrome during active duty showed silhouette measurements that are well within the normal range for area and volume."

Rothschild⁵ in 1930 reported a study of 218 cases of neurocirculatory asthenia and stated that "x-ray and fluoroscopy have contributed many interesting findings. The hearts are often small, occupying the medial portion of the chest. The left border, often extending no further to the left than the right border to the right." No measurements were given.

Master in 1943⁶ and 1944⁷ studied thirty cases confined to the slender or asthenic type of individual "with low diaphragm and small heart." He reported

From the Medical and Psychiatric Clinics and the Cardiac Research Laboratory of the Massachusetts General Hospital; and the Departments of Medicine and Diseases of the Nervous System, Harvard Medical School.

This work was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital. Received for publication Nov. 26, 1946.

that "the total transverse diameter in the posterior-anterior view is usually between 9 and 12 cm., which is definitely below the average adult size of 12 or 14 cm. or more."

Friedman⁸ in 1945 presented the size of the heart in twenty patients with neurocirculatory asthenia. He compared teleroentgenograms of these patients with those of fifteen normal young adults. He found that the average cardiothoracic ratio of the patients with neurocirculatory asthenia was 0.407 while that of the controls was 0.402. He considered the heart of his patients with neurocirculatory asthenia to be normal in size.

PRESENT STUDY

We have measured the cardiac diameters and areas of sixty-seven patients with neurocirculatory asthenia, fifty with chronic neurocirculatory asthenia, and seventeen with acute neurocirculatory asthenia; and have compared them with similar measurements of fifty healthy subjects chosen in the same age group, between 20 and 30 years of age, and also with the measurements of twenty-two young men who have been ill for a long time with tuberculosis. The division between chronic and acute neurocirculatory asthenia was made on the basis of history alone. Those who had a life-long course or who could never do hard work or engage in athletics were designated "chronic neurocirculatory asthenia;" those who gave convincing evidence of good health, ability to do muscular work or athletics, and nervous stability previous to the onset of illness were designated "acute neurocirculatory asthenia." The healthy subjects were normal hospital interns who had chest x-ray films taken incident to routine physical examination. The neurocirculatory asthenia patients were ambulatory hospital patients and were mildly active around the hospital. Previous to hospitalization they were performing various duties, mainly in military service. The patients with tuberculosis were all sanitarium patients and were relatively inactive. The x-ray photographs were taken at six feet, at maximum inspiration for the neurocirculatory asthenia and healthy control group, and during quiet breathing for the tuberculous control group. The following technique of analysis was used. A record was obtained by teleroentgenogram in the anteroposterior view.⁹ The cardiac outline was traced on drawing paper by superimposition and the following diameters were measured: transverse (*T*), long (*L*), broad (*B*), and left ventricular chord (*LV*). The area of the heart shadow (*A*) was measured by a planimeter after arbitrarily joining the outer and visible ends of the upper and lower borders by flat curves. Every area was measured three times and checked, on occasion, by other observers. The mean of the three measurements was taken.

The average measurements for the various groups are presented in Table I. This shows consistently slight, but statistically insignificant, differences between the mean diameters in chronic neurocirculatory asthenia as compared with the healthy control subjects.

The difference in heart area between chronic neurocirculatory asthenia and controls is statistically significant; however, when adjustments are made for the fact that the healthy controls were larger men than the neurocirculatory asthenia

TABLE I. COMPARISON OF CARDIAC DIAMETERS AND AREAS FROM X-RAY FILMS OF FIFTY HEALTHY CONTROL PATIENTS, FIFTY PATIENTS WITH CHRONIC NEUROCIRCULATORY ASTHENIA, SEVENTEEN PATIENTS WITH ACUTE NEUROCIRCULATORY ASTHENIA, AND TWENTY-TWO PATIENTS WITH PULMONARY TUBERCULOSIS

HEART SIZE	HEALTHY (50)	CHRONIC NCA (50)	ACUTE NCA (17)	TBC. (22)
T cm.*	12.5	12.3	12.5	11.6
B cm.	11.0	10.5	10.7	10.4
LV cm.	10.6	10.1	10.5	10.4
L cm.	14.6	14.2	14.3	14.2
Area cm. ²	111.8	102.6	107.6	98.4

Significance ratios of differences between means of healthy control subjects and chronic neurocirculatory asthenia are for $T = 1.07$, $T/TH = 0.50$, $B = 1.00$, $LV = 1.54$, $L = 1.54$, all not significant; Area = 3.33, significant.

* T refers to transverse cardiac diameter; B , the broad diameter; LV , the left ventricular chord; L , the long diameter; and TH , the thoracic diameter.

patients, even the slight differences become negligible. The adjusted heart area size per square meter of body surface (heart area in cm.²/body surface in M.²) for fifty healthy controls was 58.7 and for fifty chronic neurocirculatory asthenia patients, 56.8 (Table II); the significance ratio of the difference between these means is 1.29 and this difference is not statistically significant.

Table II summarizes the data when all diameters and areas in each case are adjusted for body surface area, using the tables of Roth,¹¹ and when transverse diameter (T) of heart is adjusted (T/TH) for thoracic diameter (TH), shows that with body size taken into account there is no adequate basis for the conclusion that neurocirculatory asthenia is characterized by a small heart. Table III demonstrates this same point in a somewhat more familiar, although mathematically less accurate, form.

Table IV presents all the data from each case for healthy controls and neurocirculatory asthenia patients. The transverse diameters are almost identical and the cardiothoracic ratios exactly the same in the two groups. The average long diameter is slightly and insignificantly greater in the controls as is also the

TABLE II. MEANS OF MEASUREMENTS OF HEART DIAMETERS AND AREAS FROM X-RAY FILMS, AFTER ADJUSTING EACH INDIVIDUAL MEASUREMENT FOR BODY SIZE

HEART SIZE (ADJUSTED FOR PATIENT'S BODY SURFACE AREA)	HEALTHY CONTROLS (50)	CHRONIC NCA (50)
T cm./M. ²	6.59	6.81
L cm./M. ²	7.65	7.84
B cm./M. ²	5.81	5.81
LV cm./M. ²	5.57	5.62
Area cm. ² /M. ²	58.70	56.83
Adjusted for thoracic diameter T/TH	0.39	0.39

TABLE III. COMPARISON OF MEAN CARDIAC DIAMETERS AND AREAS FROM X-RAY FILMS OF FIFTY HEALTHY CONTROL SUBJECTS, FIFTY PATIENTS WITH NEUROCIRCULATORY ASTHENIA, AND TWENTY-TWO PATIENTS WITH PULMONARY TUBERCULOSIS ADJUSTED FOR MEAN BODY SURFACE

MEAN HEART SIZE MEASUREMENTS	CONTROL (50)	N. C. A.* (50)	T. B.† (22)
T cm.	12.5	12.9	12.7
B cm.	11	11	11.4
LV cm.	10.6	10.6	11.4
L cm.	14.6	14.9	14.9
Area cm. ²	111.8	108.2	108.2
Mean Body Size			
Ht. cm.	177	175	174
Wt. kg.	73	69	60.7
SA-M ²	1.91	1.81	1.73

SA-M² = Body surface area in M².*All mean heart size measurements multiplied by $\frac{1.91}{1.81}$.†All mean heart size measurements multiplied by $\frac{1.91}{1.73}$.

broad diameter and the left ventricular arc. When adjustments are made for body size there is practically no difference between the two series; in fact, the cases of neurocirculatory asthenia seem to show very slightly larger hearts as far as diameters are concerned but this is not statistically significant either.

In this study the difference between the cardiac areas of the patients with neurocirculatory asthenia and those of the controls was -8.9 per cent, but after correction for body surface the difference was -3.3 per cent (Tables I and III).

In the case of the twenty-two tuberculous individuals the measurements were slightly less than those of the neurocirculatory asthenia group, but with correction, according to body size and measurements, compared closely.

DISCUSSION

It is of interest, that all averages for heart measurements were smaller in neurocirculatory asthenia than in healthy controls. However, only the heart area measurements were significantly different statistically in neurocirculatory asthenia and controls. The patients also proved to be smaller men than were the healthy controls.

When adjustments were made for body size none of the measurements was statistically different in neurocirculatory asthenia as compared with healthy controls. Of course, the question arises whether such adjustments are precisely valid. There is no question that in general larger men have larger hearts than smaller men; however, the validity of adjusting heart size for body surface area is open to some question.¹⁰

From our data, then, we were unable to show any statistically convincing evidence that demonstrated unusual heart size in neurocirculatory asthenia.

At first glance, Table I seems to provide evidence that heart size varies with the activity of the patient, since the healthy men had largest measurements.

TABLE IV. MEASUREMENTS FROM TELEROENTGENOGRAMS OF HEART DIAMETERS AND AREAS IN HEALTHY CONTROL SUBJECTS, CHRONIC NEUROCIRCULATORY ASTHENIA, AND IN ACUTE NEUROCIRCULATORY ASTHENIA

NO.	BODY MEASUREMENTS				HEART MEASUREMENTS					
	HT. (CM.)	WT. (KG.)	SURFACE AREA (M.) ²	TH. (CM.)	T (CM.)	T/TH.	L (CM.)	B (CM.)	LV (CM.)	AREA (CM.) ²
<i>Fifty Healthy Controls</i>										
1	171.5	78	1.90	32.4	14.4	.44	14.3	10.4	10.0	107.8
2	173.0	49	1.58	28.0	10.3	.36	14.0	10.3	11.5	99.9
3	180.0	75	1.94	31.8	11.4	.35	12.7	10.5	7.2	90.1
4	183.5	71	1.93	29.8	13.1	.40	15.0	12.3	11.4	125.7
5	181.5	74.5	1.94	32.4	11.4	.35	15.1	11.4	12.3	119.9
6	181.5	75	1.96	30.0	13.0	.43	15.4	11.1	11.6	120.0
7	176.5	65.5	1.82	33.6	11.8	.35	14.3	10.2	10.6	102.0
8	185.0	81	2.05	34.0	11.2	.36	15.1	10.6	13.2	116.6
9	178.0	82	1.99	31.6	12.7	.40	14.2	11.1	10.3	110.2
10	187.0	75	2.00	32.8	13.6	.41	15.3	11.2	10.2	122.5
11	175.0	65	1.79	33.4	13.2	.39	15.6	10.6	10.9	111.3
12	168.0	70	1.81	32.0	12.6	.39	13.0	10.3	8.2	89.1
13	180.0	84	2.04	33.8	13.2	.39	14.8	11.0	10.8	112.3
14	179.5	68	1.86	33.2	14.9	.44	12.6	16.6	11.2	141.8
15	184.5	68	1.89	29.1	12.3	.42	14.5	12.3	11.2	122.3
16	176.5	76.5	1.93	32.4	12.5	.38	16.1	9.2	11.0	107.9
17	164.0	65	1.71	32.6	13.6	.41	13.3	10.9	10.1	109.6
18	174.0	75	1.90	34.0	13.9	.40	15.0	11.0	10.6	116.4
19	178.0	67	1.84	32.8	12.8	.39	15.6	12.1	11.2	130.0
20	180.0	76	1.95	31.2	13.2	.38	14.0	10.8	9.7	108.8
21	168.5	64.5	1.73	32.0	12.8	.40	14.2	10.1	10.5	103.5
22	185.5	77	2.00	32.4	11.8	.36	16.1	11.1	13.6	128.9
23	185.5	87	2.11	33.4	12.8	.38	16.3	10.6	13.2	130.3
24	175.0	72.5	1.87	33.6	13.0	.38	14.1	10.9	9.7	113.0
25	183.0	78	2.00	31.4	12.0	.38	14.7	11.1	10.8	115.6
26	175.0	66	1.79	30.0	11.5	.38	13.3	10.6	9.6	98.8
27	188.0	72.5	1.97	31.2	11.7	.38	14.3	11.2	10.8	113.7
28	183.0	81.5	2.04	30.6	12.4	.41	15.5	10.3	9.5	107.3
29	171.5	70	1.84	32.8	13.8	.42	15.1	11.0	10.2	121.2
30	181.5	75	1.95	29.4	10.7	.36	13.8	10.9	10.5	103.4
31	179.0	75.0	1.94	33.0	13.8	.41	14.6	11.8	10.6	118.3
32	160.0	61.3	1.63	29.0	15.8	.47	13.7	10.1	8.8	93.1
33	170.0	80	1.92	30.0	12.5	.41	13.7	12.0	9.7	113.7
34	183.0	79.5	2.02	30.8	11.1	.36	14.4	10.6	10.3	107.6
35	180.0	90	2.10	29.4	11.1	.37	13.1	10.0	8.9	97.8
36	183.0	81.3	2.03	32.2	13.4	.41	16.4	12.2	11.7	136.7
37	182.0	76.8	1.98	33.8	12.8	.37	13.7	10.8	9.2	104.2
38	176.5	85.8	2.03	33.4	14.6	.43	14.9	10.5	8.2	108.8
39	180.0	75	1.94	30.2	12.3	.40	15.6	10.4	11.2	111.8
40	176.5	70.3	1.86	31.6	11.9	.38	13.6	10.6	9.2	95.9
41	176.5	68	1.84	33.4	12.3	.39	14.5	11.8	11.3	115.0
42	173.0	68	1.81	31.0	12.0	.38	14.2	10.1	9.6	100.0
43	180.0	70.3	1.89	31.0	11.7	.37	14.6	11.0	11.2	107.2
44	179.0	78.3	1.97	32.3	13.5	.41	14.4	11.9	11.2	124.9
45	184.0	75	1.97	31.0	11.3	.36	14.1	11.1	10.4	103.3
46	171.5	65	1.77	29.4	11.9	.40	15.2	12.3	12.4	118.4
47	175.0	72.5	1.88	29.3	12.4	.42	15.1	11.3	11.2	112.7
48	170.0	84	1.96	34.3	14.1	.41	16.0	10.6	12.2	118.2
49	175.0	68	1.83	32.5	10.9	.33	13.6	10.2	9.9	94.0
50	179.0	68	1.86	30.6	11.2	.36	15.3	10.9	10.6	108.1
Mean	177.33	75.31	1.907	31.72	12.54	.391	14.56	10.96	10.58	111.75

TABLE IV.—CONT'D

NO.	BODY MEASUREMENTS				HEART MEASUREMENTS					
	HT. (CM.)	WT. (KG.)	SURFACE AREA (M.) ²	TH. (CM.)	T (CM.)	T/TH.	L (CM.)	B (CM.)	LV (CM.)	AREA (CM.) ²
<i>Fifty Chronic Neurocirculatory Asthenia</i>										
1	160.0	51	1.51	26.8	12.0	.44	14.0	11.0	10.3	107.7
2	171.5	83	1.95	32.0	11.2	.35	14.4	9.7	10.8	105.0
3	171.0	54	1.63	29.8	10.6	.35	12.0	9.5	9.5	86.7
4	173.0	63.5	1.76	32.2	11.0	.34	12.3	9.9	9.1	86.7
5	184.0	68	1.86	29.0	11.1	.38	12.4	10.6	8.5	86.5
6	175.0	62	1.76	29.0	11.1	.38	13.5	9.7	10.0	91.9
7	172.0	74.5	1.89	33.0	11.7	.35	13.6	10.2	9.8	74.6
8	165.0	52.5	1.57	29.8	10.9	.36	11.1	9.9	9.2	80.1
9	172.5	58	1.68	31.2	11.1	.35	11.9	9.8	7.4	87.8
10	165.0	64.5	1.67	29.2	12.0	.41	14.2	10.4	10.4	101.3
11	180.0	72.5	1.90	33.2	12.5	.37	16.1	11.5	12.2	127.8
12	173.0	72.5	1.85	31.2	12.4	.39	14.1	9.7	10.1	95.5
13	163.0	62	1.67	33.4	12.1	.36	13.4	10.6	9.8	99.9
14	180.5	71	1.97	32.0	11.9	.37	13.3	10.5	9.8	94.3
15	161.5	57.0	1.59	29.8	11.6	.38	14.1	10.6	10.9	105.6
16	180.0	70.5	1.90	30.2	12.9	.40	14.3	11.2	10.8	113.4
17	166.0	59	1.67	30.2	11.0	.36	15.2	9.7	11.3	104.5
18	180.0	91.5	2.12	33.6	12.3	.37	13.6	10.4	9.2	100.0
19	165.5	76.5	1.74	30.8	12.0	.38	13.6	10.0	8.2	94.5
20	178.0	86	2.03	35.0	15.5	.44	16.0	10.8	11.3	116.8
21	165.0	49	1.52	27.2	10.8	.39	12.4	9.5	8.1	81.2
22	177.5	61	1.76	29.6	11.2	.38	13.0	9.2	8.6	84.0
23	184.0	83	2.06	31.4	12.9	.39	14.8	10.8	10.8	114.0
24	178.0	82	1.99	30.0	14.2	.47	17.2	10.3	12.7	121.0
25	162.5	54	1.56	29.8	10.8	.36	13.5	10.0	9.8	95.0
26	181.5	69.5	1.90	36.2	12.7	.35	13.9	9.9	9.0	91.2
27	172.5	67.5	1.81	31.0	12.4	.40	13.8	9.6	10.3	92.2
28	168.5	93	2.03	33.6	14.6	.43	19.2	11.0	9.9	112.0
29	166.0	62	1.69	27.8	13.5	.48	12.8	10.2	7.2	90.7
30	183.0	82	1.92	29.6	12.6	.42	14.1	11.0	9.9	106.7
31	174.0	65	1.78	29.8	10.4	.35	11.6	9.8	8.6	80.9
32	173.0	68.5	1.81	32.8	12.7	.38	14.6	10.7	10.2	110.7
33	175.0	73	1.88	32.6	12.6	.38	13.6	10.5	9.8	101.0
34	175.0	63	1.77	30.0	13.0	.43	15.4	11.7	11.9	123.4
35	177.0	74.5	1.91	33.2	13.3	.40	15.2	11.8	10.4	126.6
36	178.0	76	1.88	31.8	11.0	.34	12.7	10.8	9.8	89.8
37	170.0	62	1.72	30.8	11.8	.38	14.2	10.8	10.5	98.5
38	180.0	66	1.84	31.6	12.3	.38	15.2	11.2	12.3	116.6
39	183.0	73	1.94	31.4	12.4	.39	14.6	11.6	11.1	119.0
40	185.5	99	2.23	37.6	19.3	.40	18.7	10.9	13.1	132.2
41	175.0	65	1.80	34.0	16.0	.47	18.0	11.5	12.0	143.2
42	175.0	75	1.92	31.6	13.5	.42	14.0	11.8	9.5	116.1
43	166.0	54	1.58	30.0	13.9	.46	14.4	12.0	10.2	116.0
44	170.0	71.5	1.82	31.8	13.2	.41	15.2	12.0	10.4	125.4
45	171.0	73	1.85	31.0	11.3	.36	13.9	9.3	10.8	88.5
46	173.0	60	1.72	29.0	9.3	.32	12.8	9.0	11.6	86.7
47	162.0	53.5	1.57	29.4	11.1	.37	12.3	9.4	8.2	80.0
48	183.0	68.5	1.89	30.0	11.2	.37	15.0	10.8	10.9	111.2
49	173.0	62	1.73	30.2	11.0	.36	13.4	10.0	9.7	92.4
50	176.0	72	1.88	32.6	13.4	.41	15.4	10.2	10.56	102.5
Mean	175.20	68.54	1.809	31.18	12.31	.388	14.16	10.48	10.10	102.60

TABLE IV. MEASUREMENTS FROM TELEROENTGENOGRAMS OF HEART DIAMETERS AND AREAS IN HEALTHY CONTROL SUBJECTS, CHRONIC NEUROCIRCULATORY ASTHENIA, AND IN ACUTE NEUROCIRCULATORY ASTHENIA—CONT'D

NO.	BODY MEASUREMENTS				HEART MEASUREMENTS					
	HT. (CM.)	WT. (KG.)	SURFACE AREA (M.) ²	TH. (CM.)	T (CM.)	T/TH.	L (CM.)	B (CM.)	LV (CM.)	AREA (CM.) ²
<i>Seventeen Acute Neurocirculatory Asthenia</i>										
1	176.5	74	1.92	32.6	12.7	.38	14.3	10.1	10.7	105.6
2	175.0	59.5	1.72	31.2	13.7	.43	16.7	12.2	13.0	138.9
3	183.0	75.5	1.98	33.4	12.7	.37	14.0	11.3	9.9	107.5
4	182.0	70	1.95	31.6	12.3	.39	14.5	10.8	11.2	111.3
5	162.5	56	1.59	29.6	14.0	.47	14.6	10.0	9.6	104.4
6	173.0	73	1.86	33.6	13.1	.38	15.7	11.4	12.2	125.5
7	175.5	76	1.92	33.6	14.2	.42	16.1	11.0	11.9	121.6
8	163.0	77	1.83	33.8	13.2	.39	14.3	9.8	9.8	98.0
9	173.0	72	1.85	31.6	11.4	.36	13.2	10.0	8.8	90.1
10	183.0	77	1.98	33.2	10.7	.32	14.1	9.9	11.2	100.0
11	183.0	66	1.86	30.8	9.6	.31	13.3	10.2	10.4	91.6
12	168.0	59	1.68	32.0	12.5	.39	14.2	9.9	9.2	100.8
13	168.0	65	1.74	32.8	12.8	.39	12.8	10.8	8.6	94.8
14	175.0	66	1.80	30.4	13.1	.43	15.0	11.3	10.6	116.0
15	168.0	63	1.72	32.0	12.8	.40	13.5	11.3	10.0	107.2
16	175.0	68.5	1.82	30.8	10.7	.34	13.3	10.6	11.0	98.4
17	165.0	57	1.62	31.8	13.0	.40	14.3	11.8	10.8	117.2
Mean	173.44	67.91	1.81	32.04	12.50	.386	14.34	10.72	10.52	107.58

the inactive tuberculous patients the smallest, and the relatively inactive neurocirculatory asthenia patients had intermediate measurements. Table III, however, shows that when body size is considered along with heart measurements, the data do not provide conclusive support to the idea that heart size is automatically related to muscular activity. However, the other associated factors make the problem sufficiently complex so that this study does not conclusively demonstrate the reverse either.

SUMMARY AND CONCLUSIONS

Heart diameters measured from teleroentgenograms of sixty-seven neurocirculatory asthenia patients were all slightly smaller, but not significantly so statistically, than the heart diameters in fifty healthy men.

Heart area was significantly smaller, statistically, in patients with neurocirculatory asthenia as compared with the heart area of healthy controls.

However, the patients with chronic neurocirculatory asthenia were slightly smaller in height, weight, and surface area than were healthy control subjects.

When heart areas and heart diameters were adjusted for body surface area of each individual subject, we were unable to demonstrate any statistically significant differences between neurocirculatory asthenia and normal controls in heart area or heart diameters.

Heart sizes in healthy controls, acute and chronic neurocirculatory asthenia, and tuberculosis were not very different when adjustments were made for body size.

Our studies do not reveal statistically valid evidence for the statement that neurocirculatory asthenia is characterized by a small heart, if the body size of the individual is considered.

REFERENCES

1. Cohen, M. E., Johnson, R. E., Chapman, W. P., Badal, D. W., Cobb, S., and White, P. D.: A Study of Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome, Final Report to the Committee on Medical Research of the Office of Scientific Research and Development Under Contract OEM—cmr—157:135, 1946.
2. Lewis, T.: Medical Research Committee: Report Upon Soldiers. Size of the Heart (by Meakins and Gunson), London, 1917, His Majesty's Stationery Office.
3. Meakins, J. C., and Gunson, E. B.: Orthodiagraphic Observations on the Size of the Heart in Cases of So-Called "Irritable Heart," *Heart* 7:1, 1918.
4. Smith, B.: (a) Teleroentgen Measurements of the Heart of Normal Soldiers, *Arch. Int. Med.* 25:522, 1920.
(b) Teleroentgen Measurements of the Heart Size in Cases of Effort Syndrome *Arch. Int. Med.* 25:532, 1920.
5. Rothschild, M. A.: Neurocirculatory Asthenia, *Bull. New York Acad. Med.* 6:223, 1930.
6. Master, A. M.: Effort Syndrome or Neurocirculatory Asthenia in the Navy, *U. S. Nav. M. Bull.* 12:666, 1943.
7. Master, A. M.: Neurocirculatory Asthenia Due to Small Heart, *M. Clin. North America* 28:577, 1944.
8. Friedman, M.: Etiology and Pathogenesis of Neurocirculatory Asthenia. III. The Cardiovascular Manifestations of Neurocirculatory Asthenia, *AM. HEART J.* 30:478, 1945.
9. White, P. D.: Heart Disease, New York, 1944, The Macmillan Company.
10. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Charles C Thomas, Publisher, 1943, Springfield, Ill.
11. Roth, P.: Roth Metabolimetric Chart, 1922, Boston, Warren E. Collins.

INTERPRETING THE ELECTROKYMOGRAPH OF HEART AND GREAT VESSEL MOTION

B. R. BOONE, M.D.,* W. EDWARD CHAMBERLAIN, M.D.,† F. G. GILICK, M.D.,‡
G. C. HENNY, M.S., M.D., § AND M. J. OPPENHEIMER, M.D."

PHILADELPHIA, PA.

INTRODUCTION

THE recent development of the electrokymograph utilizing the roentgenoscope^{3,4} has provided an apparatus for the convenient recording of heart border motions in the human subject. Points on the silhouettes of the various chambers and great vessels may be selected fluoroscopically and as many cycles of motion as desired may be recorded on the standard bromide paper of an electrocardiographic recorder, with minimal cooperation from, and no inconvenience to, the subject. The resulting records are familiar in appearance.

In its functioning as the circulatory pump, the heart undergoes a continuously repeated pulsating motion. Several methods of graphically recording this motion have been devised. From these methods it has been established that each chamber of the heart and each great vessel has its characteristic motion, and that this motion is altered in the presence of cardiovascular disease.^{1,2,5,6,8,9}

Among these previous recording methods, that of the roentgenkymograph is the best known. Much good work has been accomplished by means of this particular apparatus. The electrokymograph complements the work of the roentgenkymograph. It produces records (the "electrokymogram") with adequate detail of any desired duration, and readily lends itself to the simultaneous recording of other cardiodynamic phenomena, such as the pulse (carotid), the electrocardiogram, or the stethogram. When such known phenomena are recorded simultaneously on the same time axis with the heart motions, the significant points on these familiar curves may be projected to the motion curves. The established physiologic meanings of such points, and intervals between points, thereby can be utilized in the analysis and interpretation of the electrokymographic curves.

It is accepted that the time relationships of various landmarks on the electrocardiogram are not precisely correlated with the dynamic heart cycle (opening

From the Departments of Radiology, Medical Physics, and Physiology, U. S. Public Health Service Heart Demonstrations Section, Temple University School of Medicine.

Received for publication Feb. 19, 1947.

*Senior Surgeon, U. S. Public Health Service.

†Professor of Radiology.

‡Surgeon (R), U. S. Public Health Service.

§Professor of Medical Physics.

"Professor of Physiology.

and closing of auriculoventricular, aortic, and pulmonic valves, and so forth). For example, the earliest demonstrable evidence of the isometric systolic contraction phase of ventricular activity may vary in its point of coincidence on the QRS complex. For this reason, the electrocardiogram is not particularly suitable for establishing the time relationships of the events recorded in the electrokymogram.

Heart sounds originate from mechanical events and, therefore, could be used as the "timers" of the various "events" shown by the electrokymogram. However, some technical difficulty is encountered when this is attempted. When the microphone is placed on the precordium it interferes with the alignment of the pickup unit of the electrokymograph.

We have found pulse tracings to be most satisfactory for this important work of establishing the time relationships of observed points on the heart motion curves. Theoretically, one could employ either venous or arterial pulse tracings for this purpose. From a practical standpoint we have found the carotid pulse tracing most suitable.

Multibeam recording apparatus is available, permitting simultaneous recording of a number of these cardiodynamic and bioelectric phenomena, but such instruments are not common and are expensive. Investigations with such apparatus are very desirable, but may well be assigned to the research physiologist. For the clinical radiologist or cardiologist, the commonly available, single-beam electrocardiograph will usually be the instrument of choice. When equipped with a suitable pulse recorder (carotid) and the electrokymographic pickup unit described elsewhere,² it can be used interchangeably for electrocardiography, or for records of heart border motion.

METHODS AND APPARATUS

The electrokymograph is an attachment for use with the roentgenoscope. It consists of the photosensitive pickup unit with its power supply, the carotid pulse recorder, and the recording galvanometer. The photosensitive pickup unit is mounted on the patient side of the fluoroscopic screen so that the center of the lead slit aperture is in the central x-ray beam. The carotid cup is held securely but gently over the carotid artery by means of a convenient clamp. The carotid pulse signal is conducted by rubber tubing to the recording tambour which is mounted in the lens tube of the galvanometer optical system.* The heart border motion signals from the photosensitive pickup unit are conducted to the galvanometer after passing through a filter which effectively removes the 120-cycle ripple in the output of the x-ray tube.

The technique of making an electrokymographic recording is comparatively simple, requiring nominal cooperation of the patient, no rehearsing, and only a few minutes to accomplish. It is not necessary to employ any unusual factors in the operation of the roentgenoscope. It should be operated with voltage and current settings at their usual levels. (We have obtained excellent electrokymographic records with as little as 6r per minute incident upon the patient's

*The system described here is based upon the string-galvanometer type of electrocardiograph.

skin.) The lead slit diaphragm of the phototube pickup is placed fairly close to the patient's chest wall, and is aligned so that the heart border motion which it is desired to record is at all times superimposed upon the diaphragm aperture.* The long axis of the diaphragm aperture should be approximately perpendicular to the contour of the silhouette at the point being studied (Fig. 1).



Fig. 1.—Roentgenoscopic ventral projection of patient's chest. The diaphragm only (relative size) is illustrated on two points of the patient's cardiac silhouette. Note that the long axis of the diaphragm is placed approximately in the direction of motion of the point of the heart border under investigation. As the heart goes into its contraction (dotted border) the shadow appears to move across the aperture. After the diaphragm system is properly aligned, the roentgen-ray beam is coned down by means of the roentgenoscope shutters to a small area as indicated by the dotted rectangle.

The patient stops breathing on request, and the camera is started. Usually ten heart beats are counted, after which the camera is stopped and the patient allowed to resume normal breathing. The producing of a Valsalva or Mueller respiratory effect should be avoided. The patient may be in a recumbent or upright position as the conditions of examination require. Most of our records have been made with the patient in the upright position. This makes it easy to bring the various chambers or great vessels into clear silhouette, by rotating the patient.

*It should be noted that electrokymographic records will exhibit greatest amplitude when the aperture is placed so that it is almost completely covered during the most expanded phase of the silhouette (greatest percentage change in amount of x-ray reaching the pickup device).

FACTORS IN INTERPRETATION

Electrokymographic records (Figs. 3, 4, and 5) show expansile or filling phenomena as upward moving limbs, and contractile or emptying phenomena as downward moving limbs. (The opposite could have been produced by reversal of the galvanometer leads.) Since we use standard electrocardiographic recorders, the small vertical timing lines are at .04 second intervals. The horizontal lines are 1 mm. apart, and the paper speed is 25 mm. per second. The time axis is from left to right. The steeper the slope of a limb of the curve, the more rapid the action or movement; the less steep the slope, the slower the action. Changes in slope upon a limb represent changes in speed of action, and notches or serrations represent smaller superimposed changes of action. When a curve runs parallel to the moving axis of the film, the state of no motion is indicated. Thus recorded, the movements are found to be more complex than previously thought, but lend themselves to description under two main headings: Volumetric Factors and Positional Factors.

Volumetric Factors: To a considerable extent the movements of the cardiac silhouette reflect volumetric changes. Many of the curves are surprisingly accurate replicas of cardiometer volume curves.¹⁰ In spite of their basic resemblance to volume curves (Figs. 2, 3), certain differences may be noted. On the basis of similar observations in roentgenkymography. Roesler⁷ has said, "... one cannot quite identify it with a ventricular volume curve, notwithstanding their resemblance" These variations and their causes are of great interest. They are contributed to by factors which may be described as "positional."

Positional Factors: The heart as a whole undergoes movement during ventricular systole and ventricular diastole because of its structure and its relationships to the great vessels. Early in ventricular systole the long axis of the heart shortens as the base and apex move toward each other.¹¹ At the same time, the broad axis widens somewhat and the shape of the heart has been said to move from ellipsoidal to globular. This action, as will be mentioned later, frequently produces a small outward movement of certain portions of the ventricular wall early in systole, instead of the expected inward movement that would ordinarily accompany a decrease in volume. Roesler,⁷ and Wolferth and Margolies¹¹ have clearly demonstrated this phenomenon in roentgenkymography.

In addition to the preceding, two other positional changes may be described: (1) Pendulum motion results from such factors as the straightening action of the aorta, and (2) rotation is brought about by the spiral arrangement of the ventricular muscle bundles. During systole this rotation results in ventral and cranial motion of the apex. In diastole this motion is reversed. These positional changes are superimposed on the volumetric changes, and thus cause the difficulties of interpretation mentioned by Roesler. They may be opposite in direction and have a counteracting effect; or they may be in the same direction and have an additive effect. When present, these positional changes are exhibited principally in early systole or early diastole, as Wolferth and Margolies¹¹ have pointed out in cardiometric studies.

THE CARDIAC CYCLE OF THE ELECTROKYMNOGRAM

The cardiac cycle, as has been shown by Henderson, Wiggers, Starling, and others, may be divided into a series of cardiodynamic events or phases. Graphic records of pressure changes and volume changes of the chambers of the heart are available and form the basis for our interpretation of electrokymograms.

Fig. 2 is a schematic drawing showing the application of the phases of the cardiac cycle to the ventricular electrokymogram. The carotid pulse tracing which is shown below the ventricular curve is utilized for timing. The ventricular curve shows two main components, one descending, the other ascending. Each of these is preceded by a serration. Vertical lines connect identical time points on the two curves and serve to identify the various phases of the cycle. Three of these lines (2,3, and 4) mark well-defined points on the carotid pulse tracing.

INTERPRETIVE BASIS FOR ELECTROKYMNOGRAMS

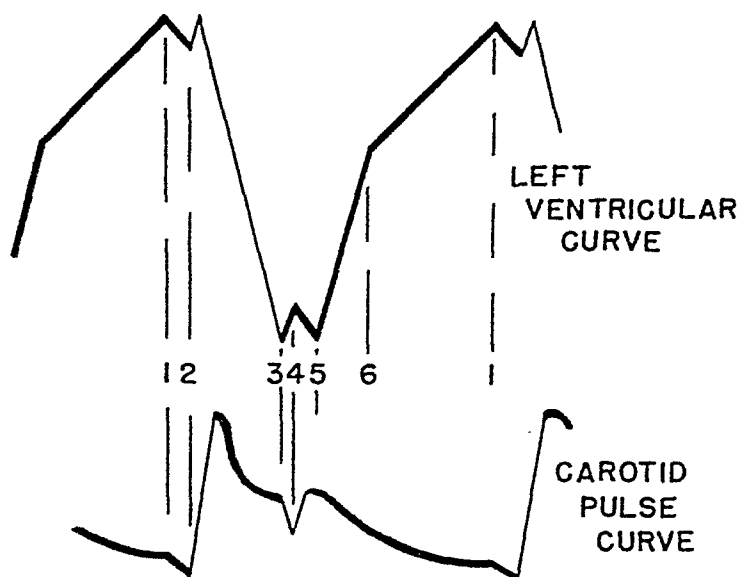


Fig. 2.—A schematic drawing of the method of interpreting electrokymograms of the left ventricular border, utilizing the carotid pulse curve for orientation. The vertical lines indicate the phases of the cardiac cycle. 1-2, isometric contraction phase; 2-3, systolic ejection phase; 3-4, protodiastolic phase; 4-5, diastolic relaxation (isometric) phase; 5-6, rapid filling phase; 6-1, slowed filling phase.

With reference to Fig. 2, the phases of the ventricular cycle are described as follows:

Isometric Contraction Phase (1-2): At Point 1 a sufficient number of ventricular fibers are in contraction to begin raising the intraventricular pressure. The mitral valve is forced shut abruptly (first heart sound) and the ventricle is a closed chamber during this phase, with no volume changes occurring. As all the fibers get into contraction the intraventricular pressure mounts rapidly

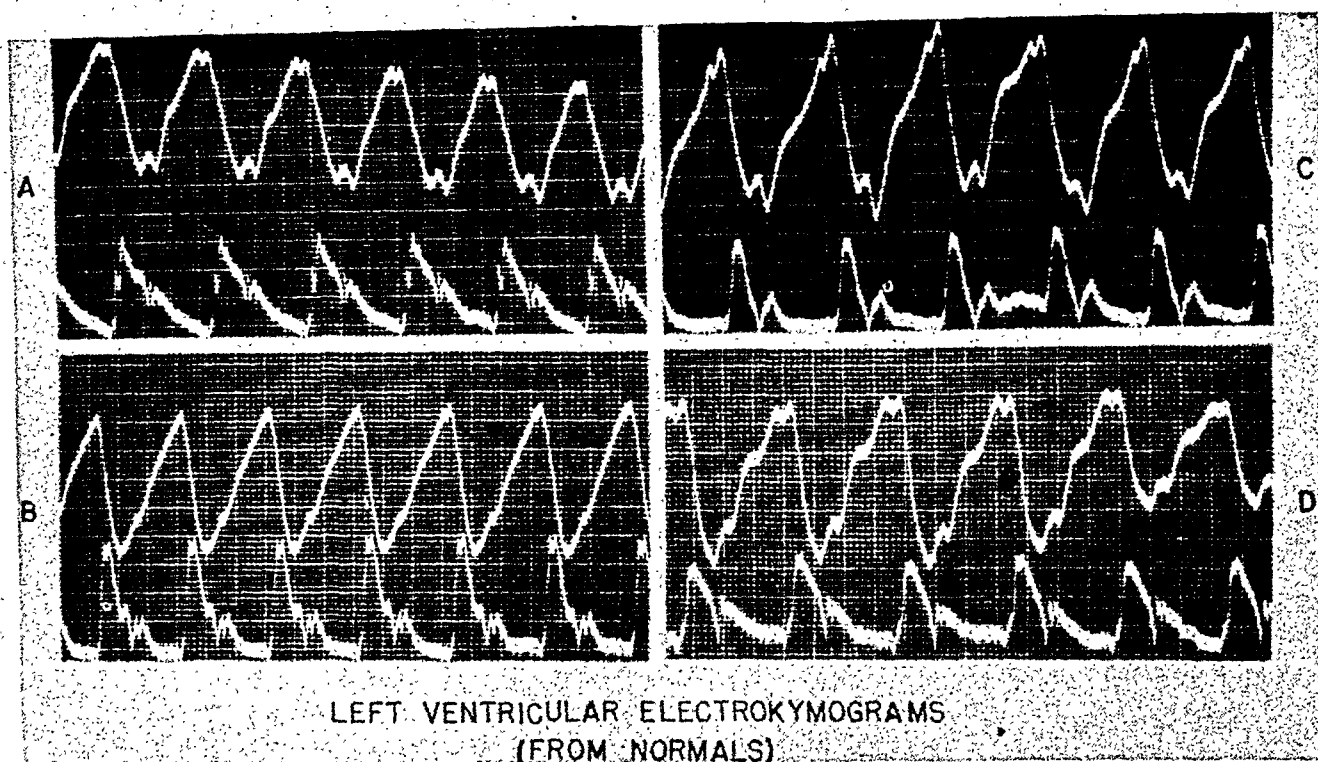


Fig. 3.—Four representative samples of left ventricular electrokymograms from normal persons. The lower curve on each sample is from the carotid pulse. By utilizing the interpretive method illustrated in Fig. 2, the various phases of the ventricular cardiac cycle may be identified.

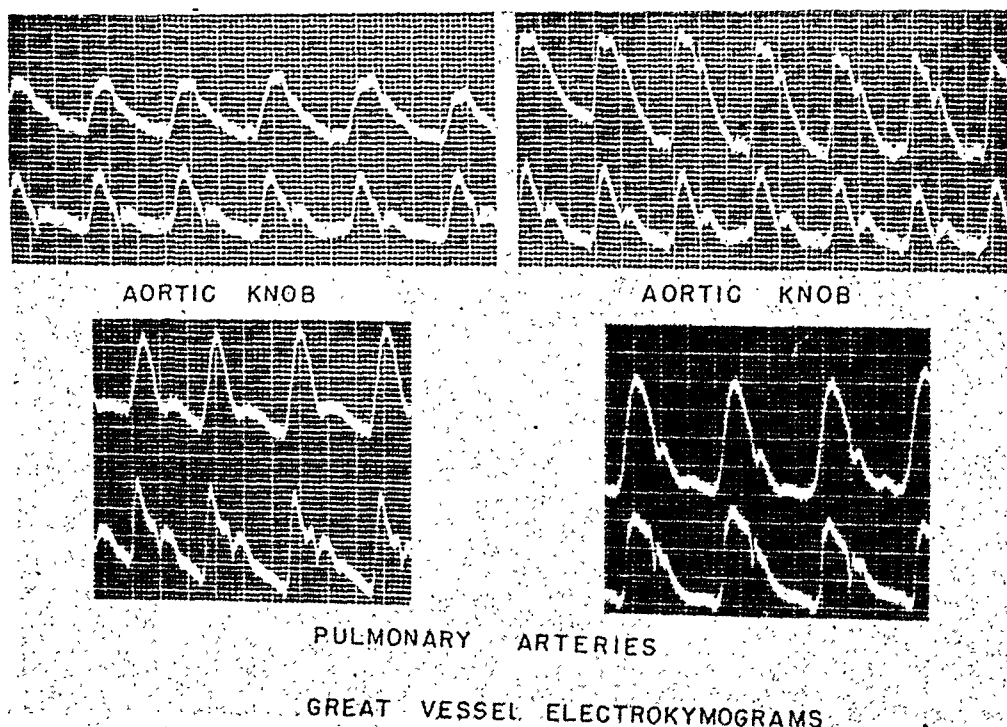


Fig. 4.—Two sample records from aortic knobs and two from pulmonary arteries. The lower curve on each sample is from the carotid pulse. Of particular interest are the similarity of the contours and the phasic relationships of the aortic knob and pulmonary artery curves to the carotid pulse curves.

until at Point 2 it becomes greater than aortic pressure and the aortic valve is forced open. While there are no volume changes prior to the opening of the aortic valve, the curve may show changes (positional) because the shape of the heart is moving from ellipsoidal towards globular, and anterior rotation and elevation of the apex are under way. The effects of such positional changes may also be evident just *after* Point 2, as the aortic valve opens.

Ejection Phase (2—3): At Point 2 the aortic valve opens, and the ventricle and aorta become continuous. Blood is ejected rapidly into the aorta. At this early point in ejection the positional factors frequently become quite prominent, the ventricular wall exhibiting a quick, brief outward motion before its major inward motion commences. The exact form of this serration at the beginning of the ejection phase will be found to differ in different individuals and at different points on the ventricular wall of a given individual. (Hirsch also has shown this in roentgenkymography.) As the end of ejection (Point 3) is approached, the flow into the aorta slows because of pressure equalization, and the down limb frequently becomes less steep, terminating at Point 3.

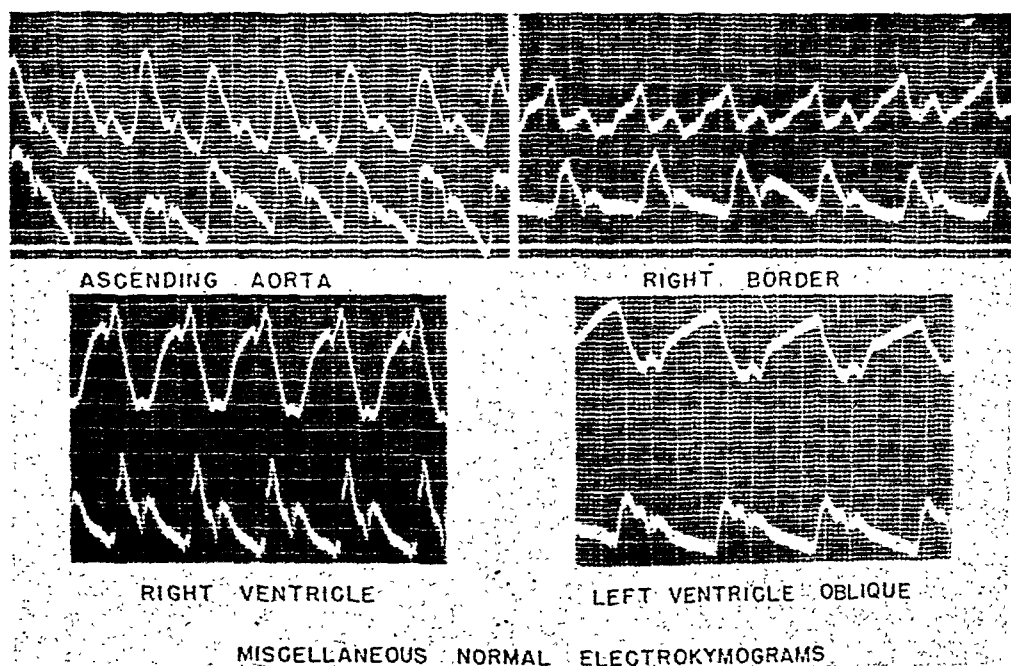


Fig. 5.—The four sample electrokymograms shown here are from the ascending aorta, the middle right border, the middle right ventricular border, and the middle left ventricular border (left oblique ventral projection), respectively. The lower curve on each sample is from the carotid pulse.

Protodiastolic Phase (3—4): At Point 3, the beginning of the pulse incisura marks the end of ventricular systolic ejection and the onset of protodiastole. This is the first phase of diastole. The incisura, Point 4, marks the closure of the aortic valve. The duration of protodiastole is approximately .04 second. Here again, the exact form of this serration will vary.

Isometric Relaxation Phase (4—5): The aortic valve has closed at Point 4, and the mitral valve is still closed. During this phase, the left ventricle is normally a closed chamber and undergoes no volume change. An upward or downward displacement in the electrokymographic curve in this phase is interpreted as a "positional change."

Rapid Diastolic Filling Phase (5—6): The mitral valve opens at Point 5 when the intraventricular pressure falls below the auricular pressure. The initial inrush of blood carries the ventricular wall rapidly outward and the electrokymographic curve is seen to rise rapidly to Point 6.

Slowed Diastolic Filling Phase (6—1): The inflow of blood slows in this period because the pressure begins to equalize. The curve, therefore, becomes less steep. In the late portion of this phase auricular systole occurs, adding an increment to the inflow. If the heart rate is relatively slow, this increment may appear on the record. If the rate is rapid, auricular systole tends to be abbreviated and little or no evidence of it is seen on the record.

Figs. 3, 4, and 5 present typical curves recorded from normal young adults. These curves, as indicated in the captions, are from the various borders of the heart and great vessels. By referring to Fig. 2, the various points and cardiac-cycle phases on these electrokymograms may be identified.

It will be noted that the electrokymographic curves from the left ventricles resemble each other in their basic patterns, but also exhibit individual variations. Individual variations also occur on the records from other parts of the heart and great vessels. These variations of the normal electrokymograms are important and are under further study.

COMMENTS

The simple mechanical method employed for recording the carotid pulse is not instantaneous as is the electrical method for recording the heart motions. Because of this it can be seen in Fig. 3 that the onset of the ejection phase of the carotid curve is slightly behind that of the ventricular curve. This lag is due to the transmission time required for the ejection impulse to travel from the left ventricle to the carotid artery plus the transmission time of this impulse from the pressure cup on the patient's neck to the recording tambour. This small lag does not lessen the value of the carotid curve for timing purposes, but must be considered when precise time measurements are desired.

An interesting application of precise time measurements is afforded by electrokymograms from the pulmonary artery and ascending aorta. Such measurements provide means of comparing the ejection time from the right ventricle with that of the left ventricle. These studies suggest that electrokymograms may prove useful in the investigation of bundle branch block.^{12,13}

Ordinarily, electrokymograms are obtained with the pickup device over some point on the border of the cardiovascular silhouette. When the device is deliberately placed so that its aperture is completely within the cardiac shadow, the cardiac cycle continues to be recorded. This occurs because changes in the thick-

ness of the heart produce changes in the amount of x-ray which reaches the pickup device. These thickness changes contribute in some measure to the record even when the aperture of the pickup device is in its conventional position over the heart shadow border. This may partly explain why electrokymograms resemble volume curves as obtained by the physiologist with the cardiometer.

CONCLUSIONS

1. A basis for the interpretation of the electrokymogram has been presented. Simultaneous recording of the carotid pulse serves to establish time-relationships.

2. Though it greatly resembles a volume curve, the electrokymogram is principally a record of the movement of that portion of the heart or vessel wall which is aligned with the pickup device. We have shown that while such movement is mainly a result of volume change, the effects of "positional change" are also present.

3. Electrograms can be obtained of any portion of the heart or great vessels which can be brought into fluoroscopic silhouette.

REFERENCES

1. Chamberlain, W. E., and Dock, W.: The Study of Heart Action With the Roentgen Cinematograph, *Radiology* 7:185, 1926.
2. Faber, B., and Kjaergaard, H.: X-Ray Kymograms of Normal and Pathological Hearts, *Brit. J. Radiol.* 9:335, 1936.
3. Henny, G. C., and Boone, B. R.: Electrograms for Recording Heart Motion Utilizing the Roentgenoscope, *Am. J. Roentgenol.* 54:217, 1945.
4. Henny, G. C., and Boone, B. R.: Improved Electrograms for Recording Heart Motion, Improved Type, *Am. J. Roentgenol.* 57:409, 1947.
5. Hirsch, I. S.: Recording of Cardiac Movements and Sounds by the Roentgen Ray (Kymophonoroentgenography), *Radiology* 22:403, 1934.
6. Hirsch, I. S.: Application of Kymoroentgenography to the Diagnosis of Cardiac Disease, *Radiology* 23:720, 1934.
7. Roesler, H.: *Clinical Roentgenology of the Cardiovascular System*, Springfield, 1943, Charles C. Thomas, Publisher.
8. Scott, W. G., and Moore, S.: Roentgenkymography: Its Clinical and Physiological Value in Study of Heart Disease, *Ann. Int. Med.* 10:306, 1936.
9. Sussman, M. L., Dack, S., and Master, A. M.: Roentgenkymogram in Myocardial Infarction. I. Abnormalities in Left Ventricular Contraction, *AM. HEART J.* 19:453, 1940.
10. Wiggers, C. J.: *The Pressure Pulses in the Cardiovascular System*, London, New York, Toronto, 1928, Longmans, Green & Co.
11. Wolferth, C. C., and Margolies, A.: Movements of Roentgen-opaque Deposits in Heart Valve Areas. II. Excursion of Apex and Base of Left Ventricle Compared With That of Left Border, *Am. J. M. Sc.* 197:197, 1939.
12. Chamberlain, W. E., Boone, B. R., Ellinger, G. F., Henny, G. C., and Oppenheimer, M. J.: Asynchronism of Ejection of the Ventricles as Measured With the Electrograms, *Federation Proc.* 6:88, 1947.
13. Ellinger, G. F., Gillick, F. G., Boone, B. R., and Chamberlain, W. E.: Electrographic Studies of Asynchronism From the Ventricles: Normal Subjects and Patients With Bundle-Branch Block, Accepted for publication.

PITRESSIN TEST OF CORONARY INSUFFICIENCY

ARTHUR RUSKIN, M.D.*

GALVESTON, TEXAS

PITRESSIN has been shown by numerous investigators to be one of the most powerful vasoconstrictors, particularly of the coronary arteries.¹⁻⁵ By the application of sensitive methods, Essex and associates¹ and Green and associates² have shown that pitressin produces a marked diminution of the coronary artery inflow in anesthetized dogs. As early as 1925 pituitrin was noted to cause marked bradycardia with increase in P-R interval, sinoauricular block, bigeminy, and T-wave changes in anesthetized dogs, effects which were compared to those of anoxemia.³ Goldenberg and Rothberger⁴ observed the effects of pitressin in unanesthetized dogs to be coronary constriction, as evidenced by visible paling of the heart. In chloralose anesthetized dogs these authors found that pitressin produced electrocardiographic changes similar to those produced by asphyxia and coronary constriction; inversion of the T-waves often accompanying the marked secondary hypertension. Dietrich⁵ confirmed the parallel findings of coronary constriction (Rein thermostromuhr) and of S-T and T-wave changes in chloralose anesthetized dogs following pitressin. Myocardial ischemia produced by six per cent oxygen inhalations, despite increased coronary flow, produced similar electrocardiographic alterations. In cats which had had coronary artery ligation one week previously, pitressin, like ouabain, exaggerated the electrocardiographic deviations already present.⁶ Focal subendocardial lesions similar to those produced by digitalis, have been produced in cats by toxic doses of pitressin. The corresponding electrocardiographic changes included auriculoventricular block, various ventricular arrhythmias, and S-T and T-wave changes of the "coronary" type.⁷ The pathologic changes may again be compared to those produced by anoxic coronary insufficiency.^{8,9}

In view of these well-known effects of pitressin in animals, the use of pitressin suggested itself as a test of latent coronary insufficiency, to differentiate true angina pectoris from other conditions associated with chest pain. The manufacturers† have strongly urged that pitressin, in ampoules of 1.0 c.c. containing 20 pressor units each, be used only subcutaneously or intramuscularly, and not intravenously. Parenteral administration of the usual doses of pitressin is not infrequently accompanied by unpleasant nausea, abdominal cramps, and a de-

Received for publication Feb. 24, 1947.

*From the Department of Medicine, University of Texas Medical School, and the Heart Station of John Sealy Hospital.

†Parke, Davis & Company, to whose scientific director, Dr. Oliver T. Kamm, we are indebted for supplies of the drug.

sire to urinate and defecate. It is for this reason that the effect of pitressin upon the human electrocardiogram has not been extensively studied.

METHOD

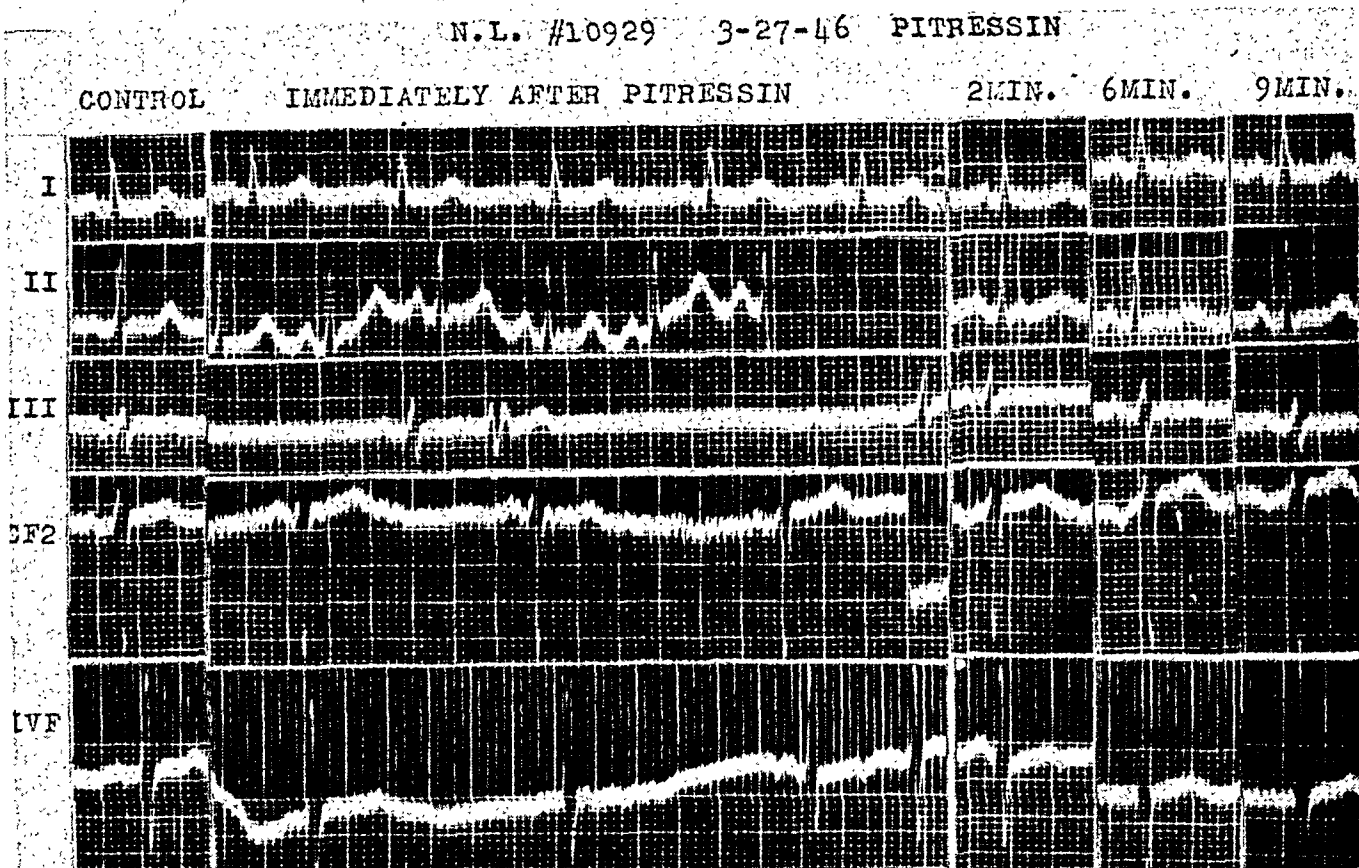
We selected for study patients considered to have angina pectoris and also patients whose suspicious symptoms were thought to be nonanginal in type. Patients with recent myocardial infarction or congestive heart failure were carefully excluded. Slowly increasing doses of pitressin were used; at first, intramuscularly, and finally, intravenously, in preliminary studies. For a subject of average weight (70 kilograms), generally satisfactory dosages were found to be 2 c.c. (40 pressor units) intramuscularly or 0.75 c.c. intravenously injected in about sixty seconds. Dosages were correspondingly adjusted for marked weight deviations. In later studies the intravenous route has been used almost entirely. Slow injection and, in cases of suspected severe coronary insufficiency, smaller preliminary parenteral dosage, are of paramount importance in preventing possible serious myocardial mishaps.

Following the injection of pitressin, the systolic and diastolic pressure usually rose 20 and 10 mm. Hg respectively, sometimes fell temporarily (that is, with bradycardia, see Fig. 1), or remained constant. Electrocardiographic changes, even in those patients with evidences of marked myocardial damage to begin with, have been limited, at most, to marked sinus bradycardia, with or without A-V nodal escape beats, premature contractions usually of ventricular origin, and S-T and T-wave shifts characteristic of coronary insufficiency (Figs. 1-4).

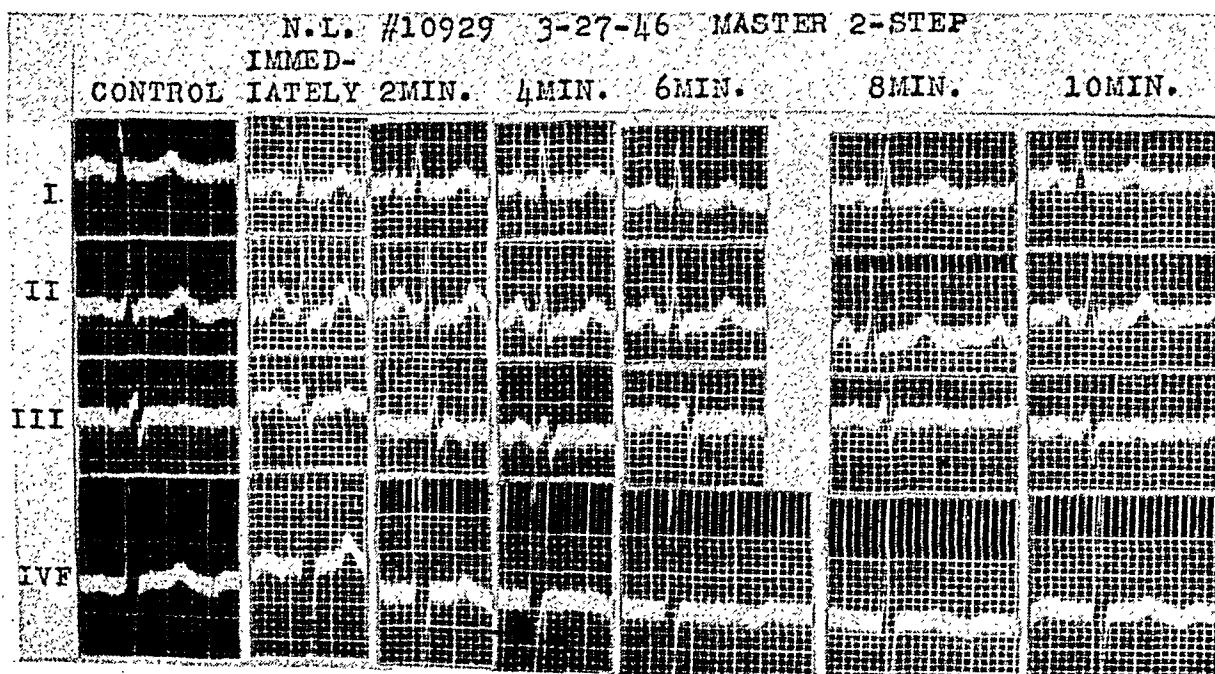
Slight precordial pain or burning ache was produced in two patients with clinical angina pectoris. A few instances of severe gagging with occasional slight vomiting were encountered in those who had just eaten and had received no preliminary sedation. Care must be taken not to employ coronary vasodilators for this purpose. Sodium pentobarbital or seconal in doses of 0.1 Gm. each were found to be satisfactory in the few instances in which they were required for proper repetition of the test. An empty stomach is a useful, but not necessary, prerequisite. All patients were able to control their desire to urinate and defecate. The abdominal cramps, when present, were slight. Pallor and coldness and, at times, burning of the face usually occurred as an immediate result of the intravenous administration of pitressin.

The time intervals for the appearance of significant electrocardiographic changes following intravenous pitressin were empirically determined to be immediately after the injection was completed, and two, six, ten, and fourteen minutes later. The same intervals may be used following intramuscular injection. Changes usually occurred within six to ten minutes, and reverted to normal after ten to fourteen minutes. Leads I, II, III, CF₂, and IVF were uniformly employed with the patient in the horizontal position, both for the control and pitressin readings.

Twelve patients with definite clinical angina pectoris on a coronary arteriosclerotic basis and ten of suspicious but indefinite "cardiac" pain in association



A.



B.

Fig. 1.—A. Pitressin test in Case 1, Table I. Clinical angina pectoris. Normal control electrocardiogram. Marked sinus bradycardia, ectopic beats, lowering of T₂, inversion of T₄ following pitressin. Test positive. B. Master test in same case. S-T₂ depressed (tachycardia?), T₄ inverted following exercise. Test positive.

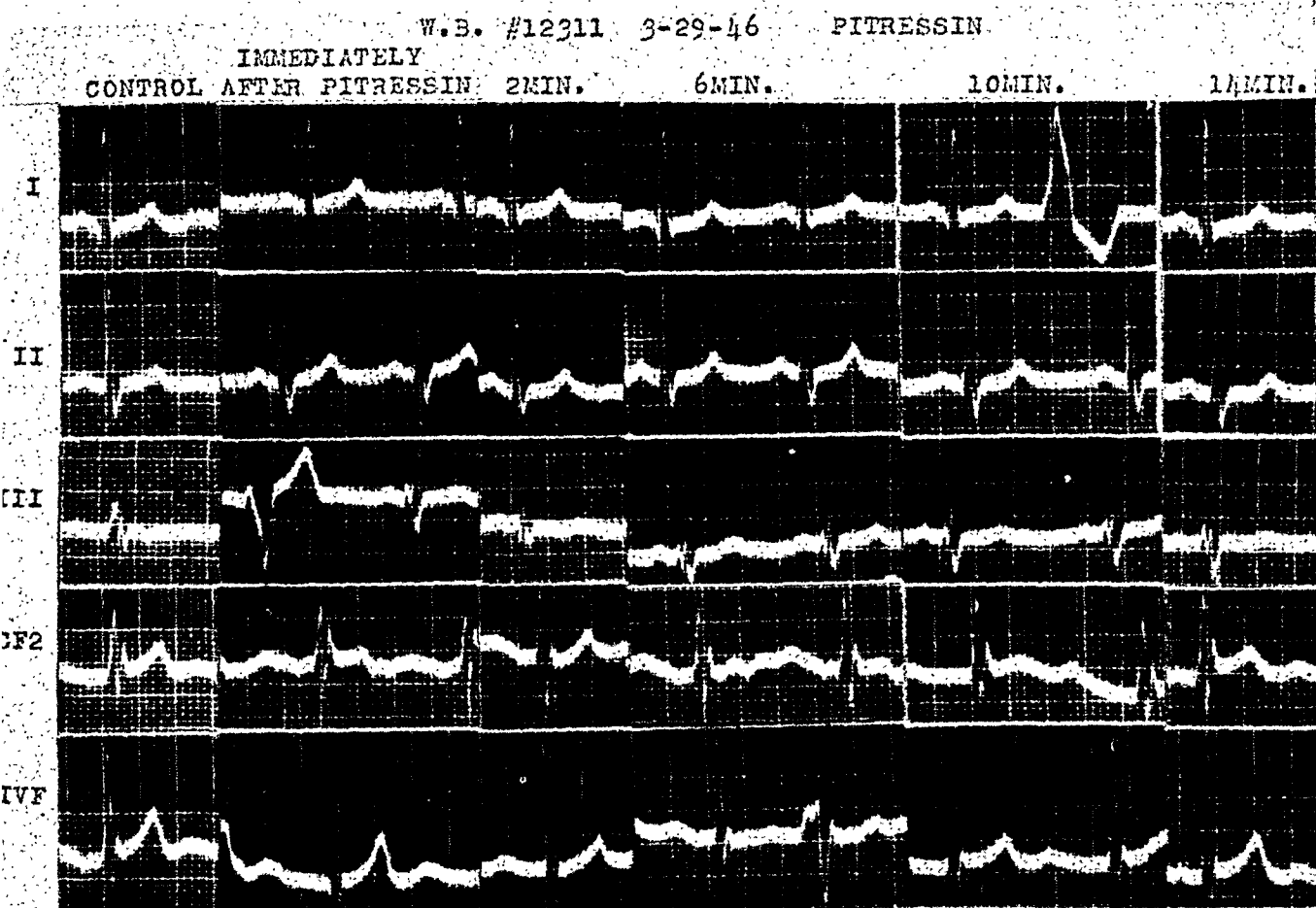
with hypertension, arteriosclerosis, syphilis, and anemia were tested both by the pitressin and the Master exercise¹⁰ tests, for purposes of comparison. Five normal controls had the pitressin test only.

RESULTS

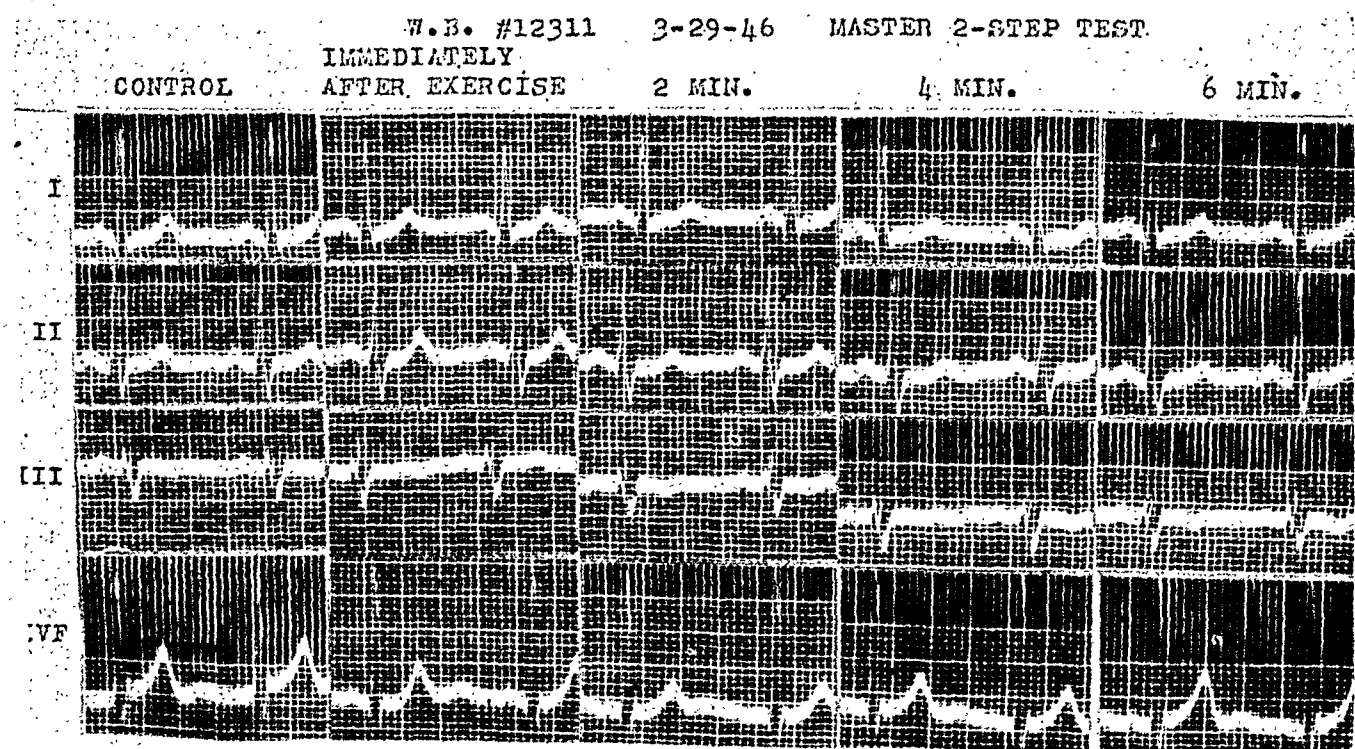
Positive electrocardiographic indications of coronary insufficiency for both the pitressin and Master tests were taken to be: (1) Change from positive T₁, T₂, or T₄ to a flat, diphasic, or negative T wave. (2) The sum of deviations (almost always downward) of the S-T segments from the controls of 3 mm. or more in Leads I, II, III, and IVF. These criteria follow the more rigid requirements of the anoxemia test of Levy and associates^{11,12} rather than those of the "two-step" exercise test of Master and associates.¹⁰ Our extensive experience with the Master test has forced us to adopt the more rigid criteria for the exercise test as well.¹³ In a patient with a previous myocardial infarction (Case 7, Table I, and Fig. 3), S-T₄ elevation was prominent. In two patients with clinical angina pectoris T waves in Leads II and CF₂ changed from positive to diphasic (Case 3, Table I, and Fig. 2). Such changes were not seen in any of the patients whose chest pain was considered to be nonanginal or in the normal controls.

TABLE I

CASE	NAME	AGE	SEX	DIAGNOSIS	BLOOD PRES- SURE	CLINI- CAL ANGINA	ECG ABNOR- MAL	PIT- RESSIN POSITIVE	MASTER POSITIVE
1	N. L.	65	F	Hyp. art. H. D.	200/120	?	No	Yes	Yes
2	E. B.	69	M	Arter. H. D.	130/70	Yes	Suggest.	Yes	Yes
3	W. B.	47	M	Arter. H. D. ?	160/100	Yes	No	Yes	Yes
4	W. C.	58	M	Arter. H. D. diabetes	120/80	Yes	Yes	Yes	Yes
5	A. S.	57	F	Arter. H. D.	180/100	?	Yes	Yes	Yes
6	F. G.	56	F	Old anterior infarct.	160/80	?	Yes	Yes	No
7	J. T.	62	M	Old anterior infarct.	160/100	Yes	Yes	Yes	No
8	L. W.	45	F	Arter. H. D. ?	140/90	?	No	Yes	No
9	G. S.	56	M	Arter. H. D.	120/75	Yes	Yes	No	Yes
10	C. M.	53	M	Old anterior infarct. ?	95/65	?	No	No	Yes
11	N. B.	68	M	Arter. H. D.	120/80	Yes	No	No	No
12	L. P.	49	M	Old posterior infarct.	135/110	?	Suggest.	No	No
13	T. B.	50	M	Duod. ulcer	120/80	?	Yes	No	No
14	A. C.	49	F	Syphilis	180/95	?	No	No	No
15	M. W.	63	F	Arter. H. D. ?	170/75	?	Yes	No	No
16	G. O.	40	F	Myelog. leukemia	110/60	?	No	No	No
17	W. S.	50	M	Duod. ulcer	130/80	??	Yes	No	No
18	B. W.	35	F	Hypertension	150/95	??	Suggest.	No	No ?
19	P. J.	48	F	Hypertension	175/120	??	No	No	No
20	M. H.	52	F	Arter. H. D. ?	125/75	??	No	No	No
21	O. T.	61	F	Pyelonephritis	140/80	??	No	No	No
22	W. K.	21	F	Sickle cell anemia	90/60	??	No	No	No
23	W. F.	62	M	Parox. tach.	150/95	??	No	No	No

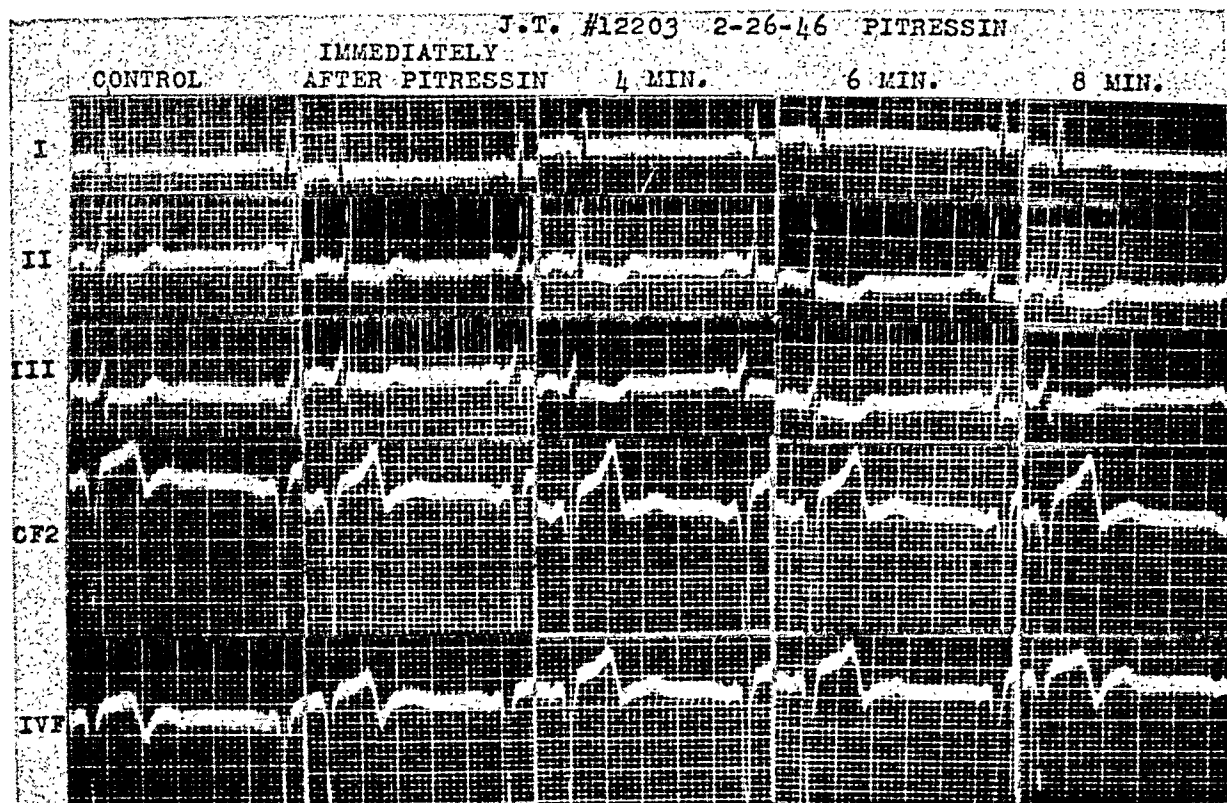


A.

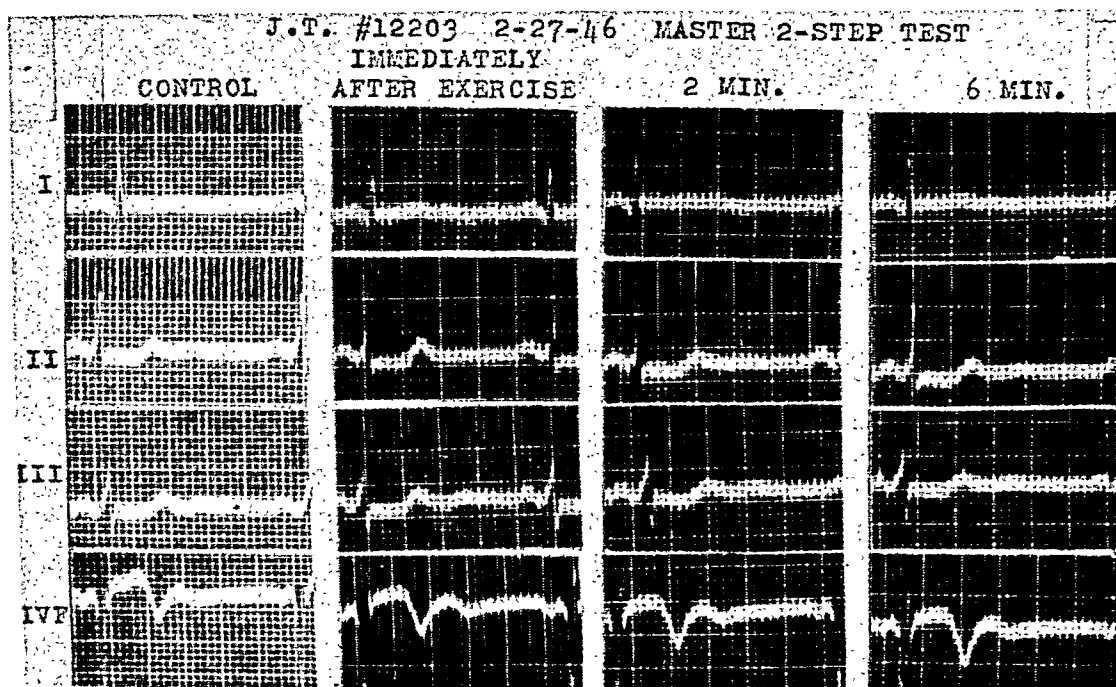


B.

Fig. 2.—A. Pitressin test in Case 3, Table I. Clinical angina pectoris. Normal control electrocardiogram. Ventricular ectopic beats, slight depression of S-T₁ and S-T₂, diphasic T in CF₂, marked flattening of T in IVF following pitressin. Test probably positive. B. Master test in same case. S-T depressions totalling over 3 mm., T₁ lower following exercise. Test positive.



A.



B.

Fig. 3.—A. Pitressin test in Case 7, Table I. Severe clinical angina pectoris. Abnormal control electrocardiogram: old (8 months) anterior myocardial infarct. Marked S-T elevations in chest leads, depressions in Leads II and III following pitressin. Test positive. B. Master test in same case. Slightly greater S-T₂ and S-T₃ depressions (2 mm.), T₄ more negative following exercise. Test negative.

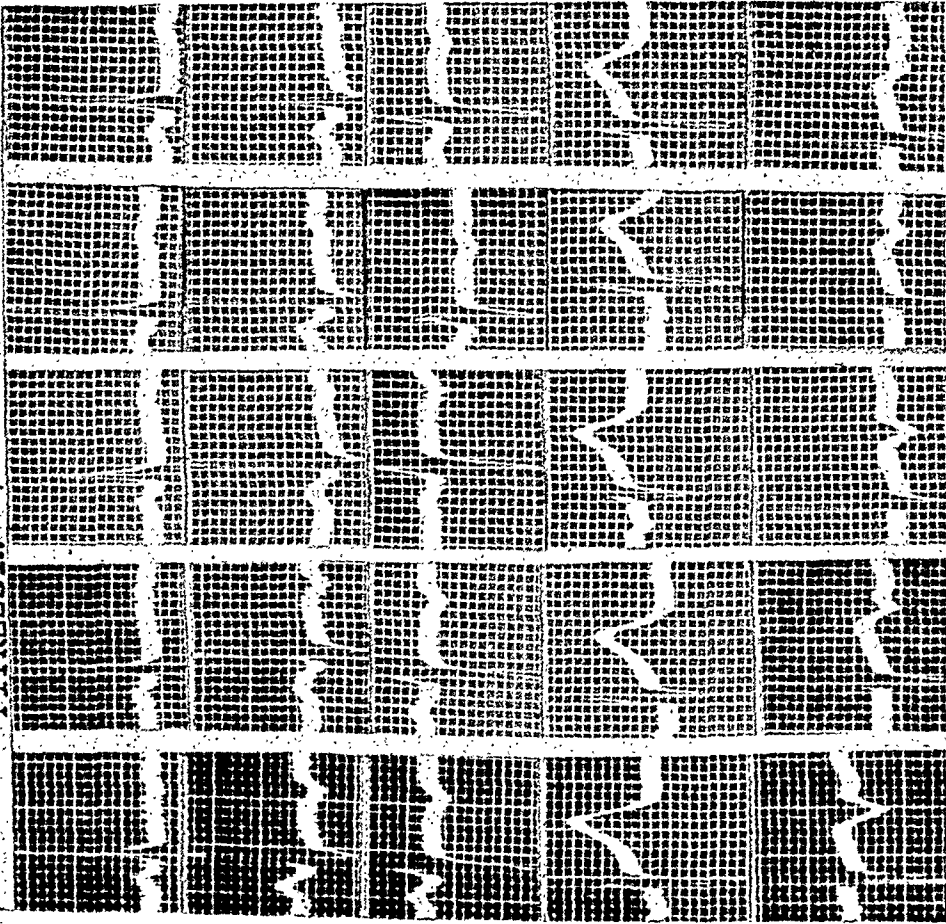
M.W. #6869 4-12-46

PITRESSIN

CONTROL IMMEDIATELY 2MIN. 6MIN. 10MIN.

AFTER

PITRESSIN



A.

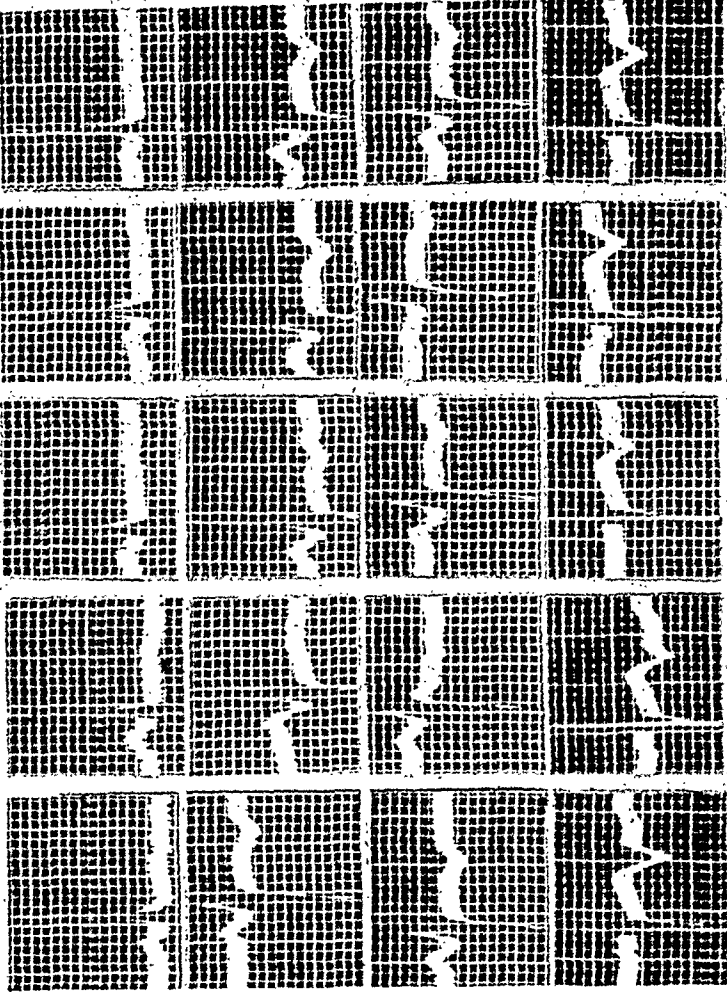
M.W. #6869 4-5-46

MASTER 2-STEP TEST

IMMEDIATELY 2MIN 6MIN. 10MIN.

AFTER EXERCISE

CONTROL



B.

Fig. 4.—A. Pitressin test in Case 15, Table I. Suspected clinical pseudoangina pectoris. Abnormal control electrocardiogram; S-T₂ and S-T₃ depressed. T₁, T₂, and T₄ negative. S-T₂ and S-T₃ less depressed, T₁ and T₂ upright, T₄ diphasic; normalization (?) of electrocardiogram following pitressin. Test negative. B. Master test in same case. Identical changes following exercise. Test negative.

Table I summarizes the results. Of the twelve patients clinically diagnosed with fair certainty as having angina pectoris, five showed positive pitressin and Master exercise tests (Cases 1 and 3, Table I, and Figs. 1 and 2, respectively). Three others showed a positive pitressin test and a negative Master test (Case 7, Table I, and Fig. 3). Two patients showed a positive Master test and a negative pitressin test; in one of these two patients the pitressin dosage (1 c.c. intramuscularly) was probably inadequate. The remaining two patients, both of whom had definite clinical angina pectoris, showed negative Master and pitressin tests. All of the patients in this group who gave negative pitressin tests showed unfavorable electrocardiographic changes, such as depression of the S-T segments, but the changes were insufficient to satisfy the preceding rigid criteria of coronary insufficiency.

All ten patients whose indefinite symptoms were not thought to be due to true angina pectoris had negative Master and pitressin tests. Some of the patients in the nonanginal group who gave negative pitressin tests presented possible favorable electrocardiographic changes, such as higher voltage of the T waves (Case 15, Table I, and Fig. 4), following both the Master and pitressin tests.

Repeated pitressin tests, provided that the same dosage was used and provided that the tests were done on different days, reproduced the same results almost exactly in most patients. Repetitions of the drug in animal experiments results in loss of the coronary vasoconstrictor effect.⁷ This should be kept in mind if repeated tests are contemplated.

COMMENT

The results which have been cited appear to establish the use of pitressin as a valid test of coronary insufficiency. The results obtained after pitressin were closely similar to the results obtained after exercise in both the clinical angina and pseudoangina groups, though the agreement was more complete in the latter group (Table I, Case 15, and Fig. 4). The pitressin test is apparently equivalent to the Master exercise test, and has the advantage that it may be used in patients unable to exercise. Even standardized exercise has extremely variable effects in the production of cardiac pain, as well as of electrocardiographic changes.¹³ This may be also true of the hypoxemia test,¹⁴ which has, moreover, occasionally resulted in some serious cerebral and other sequelae.¹¹ In patients showing marked cardiac acceleration after exercise or hypoxia, the effect on the ventricular gradient may possibly cause positional S-T and T-wave changes simulating those of coronary insufficiency.¹⁴ In these patients, too, the pitressin test would seem to be of value.

We were forced by dearth of available cases of angina pectoris to study the effects of pitressin in some patients who already presented definite electrocardiographic evidences of myocardial damage (Table I), in contrast to previous investigators^{10,11} who have studied mainly patients whose electrocardiograms were essentially normal before the test. The interesting fact, therefore, is that the same criteria of positivity and negativity of the pitressin and Master

tests can apparently be applied to these patients with abnormal tracings, as well as to patients whose electrocardiographic patterns are originally normal. This may also indicate that even in cases of marked coronary sclerosis, spasm of some arterial branches is still possible. Thus, in the group with clinical angina pectoris there were five patients in whom control or previous tracings presented T-wave negativity, S-T depression, and even left bundle branch block, (Case 5, Table I). Two of these, including the patient with bundle branch block, showed identical positive pitressin and exercise tests; two others had positive pitressin and negative Master tests; and one had the opposite findings (Table I). In the clinical group without real angina pectoris, three cases with originally abnormal electrocardiograms responded negatively to both pitressin and exercise (Case 15, Table I, and Fig. 4), as did those presenting normal control electrocardiograms. It had been assumed that cases of true coronary pain generally could be distinguished from precordial pain of noncardiac origin by the finding of electrocardiographic abnormalities, spontaneous or induced by exercise or anoxia, in the one group, and constantly normal electrocardiograms in the other group. That this assumption may be false is indicated by the preceding findings. The response to some form of relative myocardial ischemia may better distinguish the two groups.

Previous students of tests for coronary insufficiency have emphasized the need for excluding digitalis-treated patients, since digitalis modifies the electrocardiogram in the same general way as the tests do. Two patients with clinical angina pectoris who had abnormal electrocardiograms had been in congestive failure, and were taking maintenance doses of digitalis leaf (0.1 Gm. per day) at the time the tests were made. In one, the pitressin and Master tests were both positive; in the other, the Master test was positive, the pitressin test (1 c.c. intramuscularly, inadequate dose?), negative. Further studies will be necessary to show that control electrocardiograms modified by digitalis do not actually interfere with tests of coronary insufficiency. On the other hand, latent coronary insufficiency not due to coronary disease, as in severe anemia (Cases 16 and 22, Table I), apparently is less liable to become manifest in the exercise or pitressin tests. The electrocardiographic changes in the two cited cases of anemia were suggestive but not diagnostic of coronary insufficiency by our criteria.

Cases with systolic (up to 200 mm. Hg) or diastolic (up to 120 mm. Hg) hypertension, of which there were six in the angina group, and four in the non-angina group, showed a response that was similar to the response shown by non-hypertensive patients (Table I). The effects of pitressin were no more untoward in the hypertensive patients than in others, even though the blood pressure, especially the systolic pressure, usually rose somewhat higher than in patients with normal blood pressure. Positive pitressin tests were obtained in those rare cases in which the blood pressure fell (for example, 160/100 to 80/40 temporarily in Case 8, Table I), as in the majority in which it rose. Apparently the coronary constrictive effect of pitressin overcomes any increase in coronary flow which may be due to a rise in aortic blood pressure.

While there is some disagreement as to the degree to which pitressin affects the heart through the vagus nerve,¹⁶ direct myocardial effects (for example,

modification of cardiac output) have practically been excluded for nontoxic doses in animals.² In man, pitressin actually decreases the cardiac output in the first ten minutes after its parenteral injection¹⁷ or during the approximate duration of the electrocardiographic changes which have been described. This is in direct contrast to epinephrine,² which was formerly used as a test for relative coronary insufficiency on the basis that it increased the cardiac work to a greater extent than it increased the coronary blood flow.¹⁸ Exercise presumably has the same effects, and the "two-step" test the same basis, as the epinephrine test. Even eating apparently involves increased cardiac demands sufficient to produce electrocardiographic abnormalities in cases of coronary sclerosis.¹⁹ Instead of such an indirect effect, pitressin produces relative myocardial ischemia through direct coronary vasoconstriction, in which it excels other similar drugs.¹

SUMMARY AND CONCLUSIONS

1. Pitressin, a well-known coronary artery constrictor, has been utilized in doses of 0.75 c.c. (15 pressor units) intravenously, or 2 c.c. intramuscularly, for the electrocardiographic demonstration of coronary insufficiency.

2. The criteria of a positive test have been taken to be change of a positive T₁, T₂, or T₄ to a flat, diaphasic, or negative T wave, or S-T segment deviations totalling 3 mm. or more in Leads I, II, III, and IVF. These criteria may be modified by future experience. Changes in Lead CF₂ need further evaluation.

3. Close parallelism was noted in the results of the pitressin and Master exercise tests in both the positive and negative cases.

4. Of twelve patients with clinically typical angina pectoris, the pitressin test was positive in eight, or 66 per cent. In five of these eight patients the Master test was positive; in three, negative.

5. In ten patients with atypical precordial pain and five normal controls, the test, confirmed by the Master test in the former group, was negative.

6. Positive tests confirm the clinical suspicion of coronary pain; negative tests do not exclude it.

7. The side-effects of pitressin render its general use as a test for latent coronary insufficiency inadvisable. In the hands of experienced investigators it may be useful in the evaluation and management of coronary sclerosis, particularly in younger individuals, and for experimental purposes. Pitressin must not be used without thorough training in its pharmacologic effects in ascending doses, and in the estimation of the degree of coronary insufficiency by all other modern methods. Otherwise serious and even fatal myocardial ischemia and necrosis may result.

8. The results of the use of pitressin attest both coronary spasm and relative myocardial ischemia as theoretical bases for clinical anginal pain.

REFERENCES

1. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, *AM. HEART J.* 19:554, 1940.
2. Green, H. D., Wegria, R., and Boyer, N. H.: Effects of Epinephrine and Pitressin on the Coronary Artery Inflow in Anesthetized Dogs, *J. Pharmacol. & Exper. Therap.* 76: 378, 1942.

3. Resnik, W. H., and Geiling, E. M. K.: The Action of Pituitary Extract on the Heart of the Unanesthetized Dog, *J. Clin. Investigation* 1:217, 1925.
4. Goldenberg, M., and Rothberger, C. J.: Experimentelle Beiträge zur Theorie der Angina Pectoris, *Ztschr. f. d. ges. exper. Med.* 16:1, 1931.
5. Dietrich, S.: Blutversorgung und Aktionsström des Herzens, *Ztschr. f. d. ges. exper. Med.* 90:689, 1933.
6. Mulinos, M. G., and Leslie, A.: Studies on Coronary Occlusion. III. The Effect of Digitalis on the RS-T Segment of the Electrocardiogram After Coronary Ligation, *AM. HEART J.* 24:671, 1942.
7. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. V. Comparative Effects of Toxic Doses of Digitalis and of Pitressin on the Electrocardiogram, Heart, and Brain, *AM. HEART J.* 27:96, 1944.
8. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. VI. Comparative Effects of Toxic Doses of Digitalis and of Prolonged Deprivation of Oxygen on the Electrocardiogram, Heart, and Brain, *AM. HEART J.* 27:108, 1944.
9. Büchner, F., Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz, Leipzig, 1935, Georg Thieme.
10. Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C., Jr.: The Electrocardiogram and the "Two-Step" Exercise: A Test of Cardiac Function and Coronary Insufficiency, *Am. J. M. Sc.* 207:435, 1944.
11. a. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. E.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, *AM. HEART J.* 21:634, 1941.
b. Patterson, J. E., Clark, T. W., and Levy, R. L.: A Comparison of Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients With Coronary Sclerosis, *AM. HEART J.* 23:837, 1942.
12. Pruitt, R. D., Burchell, H. B., and Barnes, A. R.: The Anoxia Test in the Diagnosis of Coronary Insufficiency: A Study of 289 Cases, *J. A. M. A.* 128:839, 1945.
13. Ruskin, A., and Decherd, G.: Unpublished observations.
14. Biorck, G.: Anoxemia and Exercise Tests in the Diagnosis of Coronary Disease, *AM. HEART J.* 32:689, 1946.
15. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient. II. Factors Which Affect Its Manifest Area and Its Relationship to the Manifest Area of the QRS Complex, *AM. HEART J.* 25:23, 1943.
16. Sawyer, M. E. M., and Ettinger, G. H.: The Cardiac Action of Posterior Pituitary Extract in Physiological Doses, in the Normal Dog, and After Partial and Complete Denervation of the Heart, *Canad. J. Research, Sect. D.* 21:311, 1943.
17. Grollman, A., and Geiling, E. M. K.: Cardiovascular and Metabolic Reactions of Man to Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin and Pitocin, *J. Pharmacol. & Exper. Therap.* 46:447, 1932.
18. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: Use of Epinephrine as a Diagnostic Test for Angina Pectoris, With Observations on Electrocardiographic Changes Following Injections of Epinephrine Into Normal Subjects and Into Patients With Angina Pectoris, *Arch. Int. Med.* 45:191, 1930.
19. Simonson, E., McKinlay, C. A., and Henschel, A.: Effect of Meals on the Electrocardiogram of Cardiac Patients, *Proc. Soc. Exper. Biol. & Med.* 63:542, 1946.

Clinical Reports

ARACHNODACTYLIA AND CARDIOVASCULAR DISEASE — REPORT OF AN AUTOPSIED CASE WITH A SUMMARY OF PREVIOUSLY AUTOPSIED CASES

HAJIME UYEYAMA, M.D., BERKELEY, CALIF., AND BENJAMIN
KONDO, M.D., AND MAURICE KAMINS, M.D.
LOS ANGELES, CALIF.

INTRODUCTION

SINCE the original description by Marfan¹ in 1896 of arachnodactylia, many facets have been added to the clinical syndrome. The syndrome is characterized by an abnormal lengthening and thinning of the fingers and toes as well as the long bones, increased height, asthenic body build, dolichocephalic head with old-appearing features, funnel-shaped chest, kyphosis, and dislocation or subluxation of the lens of the eye. Numerous reports have appeared to indicate that the cardiovascular system also may be involved.

Earlier descriptions have included cardiovascular abnormalities.¹⁻⁶⁰ Specific clinical diagnoses have been made of congenital anomalies. These anomalies include patent foramen ovale,^{4,5,10,42} patent interventricular septum,⁴⁶ and patent ductus arteriosus.⁴³ Other reports have included mitral insufficiency,^{37,45} pulmonic murmurs,^{30,32} cardiac enlargement,^{7,31} hypertension,²¹ aortic regurgitation,^{31,50,56,57} aortitis,⁴¹ and atheroma of the pulmonary artery.⁴³

Rados⁵⁴ in his excellent summary of 204 cases reported up to 1940 listed sixty-three cases in which the cardiovascular system was involved. Cardiovascular abnormalities were second in frequency to ophthalmic complications.

In 1943, Baer, Taussig, and Oppenheimer⁵⁶ described two cases of sudden death in young arachnodactylic adults. At autopsy both patients were found to have medionecrosis of the aorta. In one of the two patients an aneurysm was present, but no aortic rupture had occurred. In the same year, Etter and Glover⁵⁷ described a case in which dissecting aneurysm and rupture occurred in a 21-year-old man, but did not mention the presence of medionecrosis.

The case reported in this communication is one of arachnodactylia and dissecting aortic aneurysm with rupture in which histologic studies revealed medionecrosis. This case fills a gap between the two cases of Baer, Taussig, and

From the Cardiovascular Clinical Research Laboratory, Department of Medicine, University of Southern California Medical School, and the Japanese Hospital, Los Angeles, Calif.
Received for publication Sept. 9, 1946.

Oppenheimer, which had medionecrosis without rupture, and the case of Etter and Glover, which grossly demonstrated dissecting aneurysm and rupture but did not include a description of medionecrosis. The infrequency of reports of involvement of the great vessels in arachnodactylic cases merits the presentation of an additional case.

CASE REPORT

The patient was an unmarried Japanese (Fig. 1) who was born in California on April 29, 1921. His past history was normal except for frequent childhood attacks of tonsillitis. He reached the twelfth grade in school. The family history is noncontributory. The patient had been doing heavy physical work without difficulty.



Fig. 1.—Photograph of the patient demonstrating the arachnodactylic habitus.

In August, 1942, the present illness began with severe, agonizing, compressing pain over the anterior chest, the epigastrium, and under the left scapula; the patient stated that the pain was not relieved by injections. The pain gradually subsided over a period of two weeks. He stated that the physicians thought his liver was enlarged and they attributed the pain to this enlargement. A posteroanterior chest film taken at the time revealed enlargement of the heart, and a diagnosis of rheumatic heart disease with cardiac enlargement was made (Fig. 2).

In September, 1942, the patient was transferred to the Granada War Relocation Center at Amache, Colorado. Because of his history and the diagnosis of rheumatic heart disease, he was

kept in bed and was frequently examined by various physicians. Except for an occasional pulse rate of around 96 per minute and one temperature reading of 99°F., his temperature, pulse, respiration, and blood pressure readings remained within normal limits. His only symptoms were slight pain over the left scapula and over the precordium on Oct. 14, 1942.

The patient was first seen by one of us (H. U.) on Nov. 5, 1942. He was in bed but had no particular complaints. Pulse rate was 68 per minute; blood pressure, 120/80; and temperature, 96° Fahrenheit. There was a sinus arrhythmia. The apex beat was palpated in the midclavicular line. Since no murmurs were heard, the diagnosis of rheumatic heart disease was questioned. The sedimentation rate (Cutler) was 19 mm. in one hour. The blood count showed a hemoglobin of 92 per cent and 4,160,000 erythrocytes and 8,500 white blood cells. On March 4, 1943, the sedimentation rate had dropped to 14 mm. in one hour.

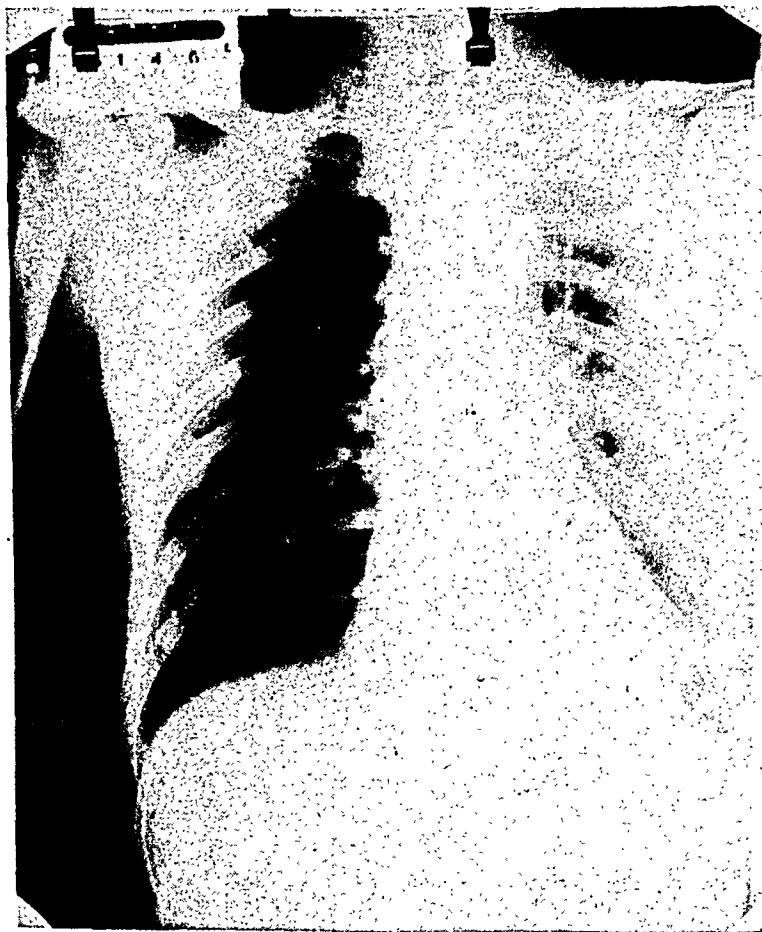


Fig. 2.—Posteroanterior roentgenogram of the chest taken August 6, 1942. Note the early enlargement of the aortic arch.

By January, 1943, the patient felt well and was ambulatory. There was no dyspnea. The only remaining sign was tachycardia with exertion. On April 2, 1943, when fluoroscopy revealed diffuse enlargement of the thoracic aorta, he was hospitalized for investigation.

Physical examination revealed an asthenic, pigeon-breasted Japanese man of 21 years (Fig. 1). The temperature was 98° F.; the pulse rate, 88; and the respirations, 19 per minute. The skin and mucous membranes were normal. The teeth were in fair condition. The tonsils were out and the uvula was missing. The tongue was normal. External examination of the eyes was negative. No glasses were used, vision was good. The pupils reacted normally to light and accommodation. There was no tracheal tug.

Examination of the chest revealed a diffuse pulsation over the left precordium. The apex beat was 11 cm. from the midline. The percussion note was normal in the second right intercostal space. A loud, rough systolic murmur was heard over the entire precordium; it was most marked at the apex and was transmitted to the left axilla. The blood pressure was 120/80 in both arms, and 144/100 in both legs. A systolic murmur was heard on both sides of the thoracic and lumbar spines, louder on the left side. There was dullness to percussion to the left of the thoracic spine.

The extremities were slender and long. The blood Wassermann was negative on April 3, and April 13. The sedimentation rate on May 4 was 16.5 mm. in one hour. On April 4, a routine urinalysis was normal. Blood counts on April 3 and May 4 were essentially the same as before. The arm-to-tongue circulation time using 5 c.c. of 10 per cent magnesium sulfate solution was 14 seconds. X-ray films showed enlargement of the aortic shadow (Fig. 3). Except for a low-grade fever, the patient was asymptomatic during his hospital stay. On May 11, 1943, he was sent home with the recommendation that bed rest be continued.

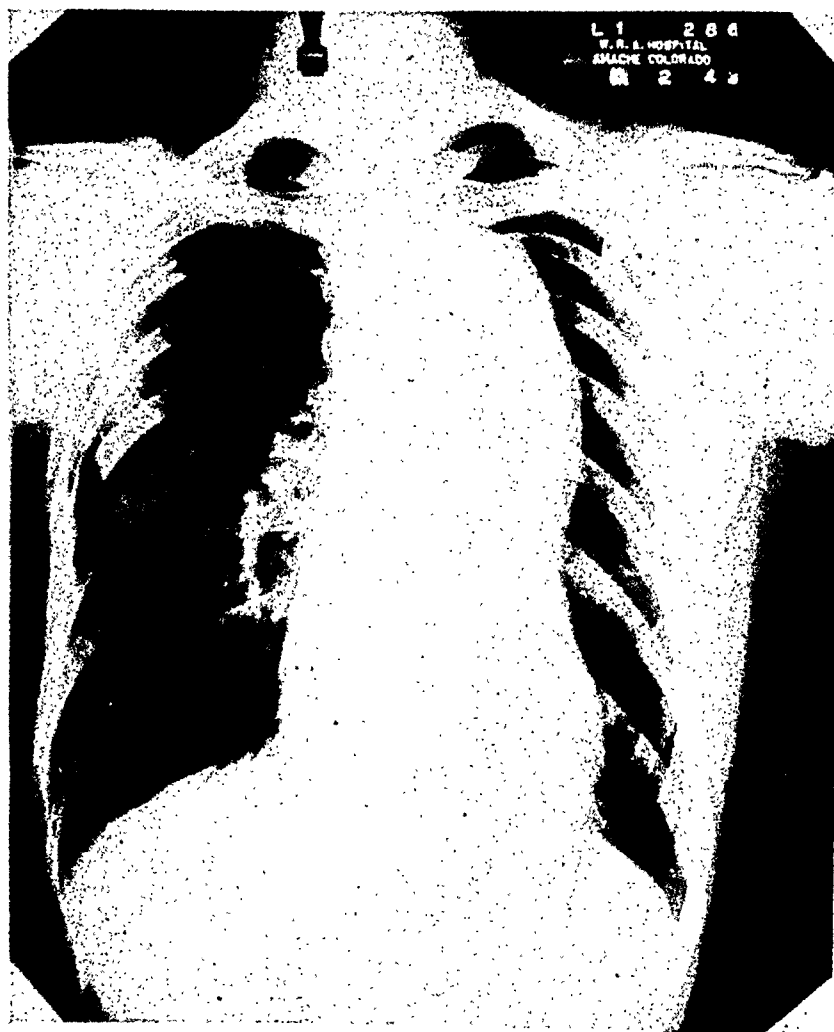


Fig. 3.—Posteroanterior roentgenogram of the chest taken April 2, 1943 (7 months after Fig. 2), showing rapid enlargement of the aortic shadow.

At home he rested most of the time. On Jan. 8, 1944, his father thought he had fever, but he was not sick enough to notify the hospital. On January 11, the patient walked to the latrine and then to the mess hall, some thirty yards away. He ate breakfast in bed at 7:30 A.M. At 8:30 A.M., while reading in bed, he suddenly expired.

*Autopsy.**—On gross examination (Fig. 1) the body was seen to be that of a 22-year-old Japanese man. His length was 178 cm. and his weight 45,359 grams. The body was very pale. The lower jaw protruded. The thyroid appeared enlarged because of an anterior convexity of the cervical spine; however, it was found to be of normal size when examined. The patient was pigeon-chested, had round shoulders, and the wings of the scapulae hung rather low. The hands and feet were spider-like. The middle finger of the right hand was 10.5 cm. long; the metacarpal bone 8 centimeters. The right foot was 27.5 cm. long; it was 7.5 cm. wide at the phalanx, and 5 cm. wide at the heel.

The cardiovascular system is shown in Fig. 4. The pericardium was smooth and shiny. The cavity contained 150 c.c. of serous fluid. The heart appeared large and dilated; its weight was 510 grams. Externally, a large aneurysm involved the transverse, descending, and abdominal aorta. It had a total length of 27 centimeters. On the left lateral border, 5 cm. distal to the origin of the aneurysm, was a perforation 3 mm. in diameter. When the chambers of the heart were opened, a slight thickening of the anterior cusps of the mitral valve with slight increase in the size of the chordae tendineae proximally was seen. The left ventricle was 12 mm. in thickness and appeared dilated. Examination of the aortic cusps showed fenestration of the margins. The coronary arteries were elevated 1 cm. above the level of attachment of the aortic valves. The proximal portion of the aorta was 4.5 cm. in circumference and, at a point 11 cm. distal to the aortic orifice, the diameter was narrowed to 2.5 centimeters. Distal to the constriction was an extensive dissecting aneurysm through which there had developed a well-established secondary channel. This secondary channel in the aortic wall communicated with the aortic lumen at the proximal and distal portions of the dissecting aneurysm.

The left chest contained 3 liters of blood. The apex of the left lung contained several small areas of indurated and scarred tissue. The pulmonary vessels were normal. The liver and spleen, and the gastrointestinal, and genitourinary systems were essentially within normal limits. The extremities were elongated and thin.

Microscopic Examination.—Very few round cells and an occasional polymorphonuclear leucocyte appeared in the vicinity of a few epicardial vessels. Some myocardial fibers were hypertrophic. In the left ventricle one small segment beneath the endocardium showed a slight degree of round cell infiltration. An occasional round cell was found interstitially in various places, although these latter cells were so few as hardly to constitute true inflammation. The myocardium, endocardium, and epicardium, in the vicinity of the base of the mitral leaflet, showed a marked degree of round cell and polymorphonuclear infiltration. The round cells predominated and were of all types from small lymphocytes to large mononuclears. These were most numerous in the myocardium. There was a marked degree of fibrosis at the base of the mitral leaflet with some areas of degeneration and possibly fibroblastic proliferation on what appeared to be the upper leaflet surface. In parts of the leaflet base, there was an increase in the capillaries with slight perivascular round cell infiltration. No Aschoff bodies or other specific inflammatory lesions were noted. More peripheral portions of the leaflet, although superficially showing what appeared to be a slight degree of degeneration and acellularity without any thrombus or active inflammatory reactions, were of increased thickness, suggestive of old inflammatory change.

The intima in the first portion of the aorta showed areas of hyalinization and intimal thickening. There were a few scattered areas of round cell infiltration. The rest of the aorta appeared somewhat edematous in places; however, it showed no specific inflammatory reaction. The aorta was thicker than expected in an individual of this age. There were no atheromatous changes. Some areas of the adventitia were more densely fibrous than normal, but there was no round cell infiltration in these areas. There was marked necrosis and loss of cell structure at the site of the tear between the original aortic lumen and the adjacent aneurysm wall. These changes extended into the aortic wall itself to a moderate degree. The outer aneurysm wall consisted of dense, fibrous tissue containing a moderate number of capillaries, around a few of which were small round cells. There was, however, very little active inflammation. Syphilitic changes were completely absent

*The gross pathologic examination was performed by Doctor H. Higa and Doctor H. Uyeyama. Pathologic examination of the tissues was performed at the Fitzsimmons Hospital Laboratory, Denver, Colo., by Captain Sion Holley.

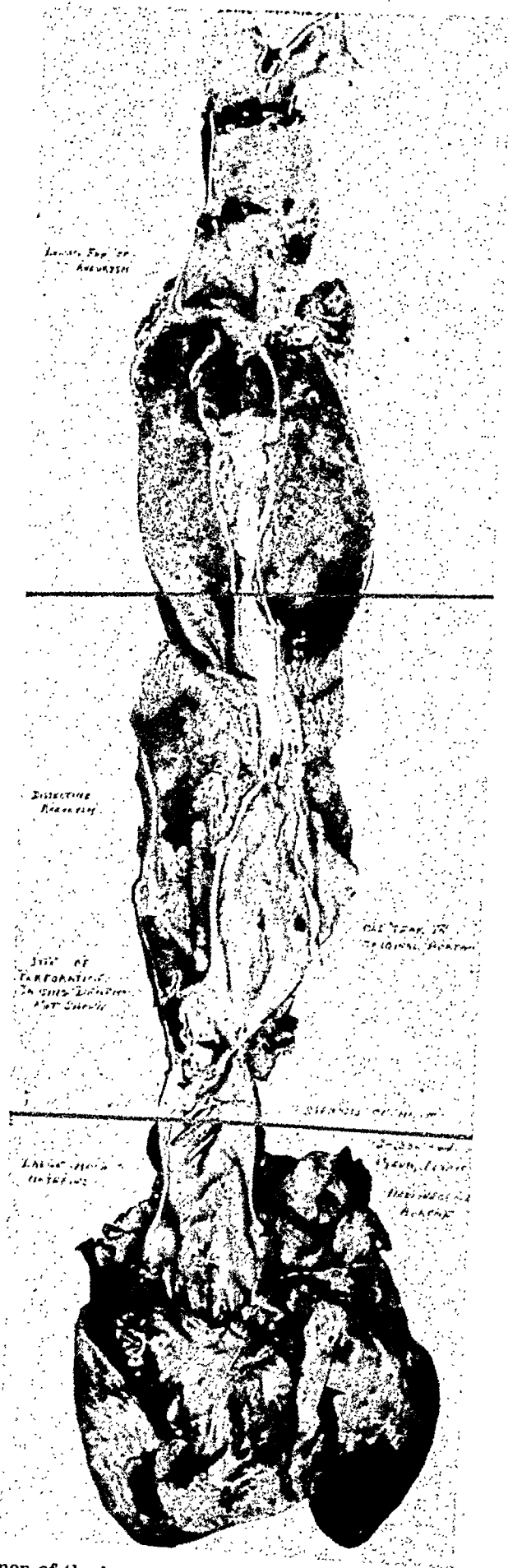


Fig. 4.—Specimen of the heart and aorta showing the extensive dissection of the aorta and fenestration of the aortic leaflets.

TABLE I. SUMMARY OF AUTOPSIED CASES FROM THE LITERATURE

AUTHORS	YEAR	AGE	CLINICAL AND LABORATORY FINDINGS	AUTOPSY FINDINGS	MODE OF DEATH AND REMARKS
Salle	1912	1½ mo.	Pulmonary systolic murmur	Patent foramen ovale	Terminal pneumonia
Boeger and Von Pfandler	1914	1 yr.	—	Patent foramen ovale	Terminal pneumonia
Piper and Irvine-Jones	1926	1¾ yr.	Systolic thrill left second and third intercostal spaces; systolic and late diastolic murmur. ECG—Sinus tachycardia with slight left axis deviation	Patent foramen ovale	Terminal pneumonia
Weill	1932	47 yr.	Not described	Mitral valvulitis	—
		27 yr.	Not described	Sacculation of aortic leaflets, dilatation of aorta	—
Rambar and Denenholz	1939	2½ yr.	Heart sounds normal	Slight edema of interstitial tissue of myocardium; myofibrils, aorta, and coronary vessels normal	Terminal pneumonia
Olcott	1940	16 yr.	Systolic precordial murmur, basal pulmonary râles	Fenestration of mitral valve with mitral endocarditis. Coronary arteries normal, aorta small with a few fatty patches on the intima	Endocarditis and terminal pneumonia

Bergstrand	1943	1 mo.	Heart sounds clear, no murmurs	No abnormal cardiac findings	Terminal bronchopneumonia
Etter and Glover	1943	21 yr.	Systolic and diastolic aortic murmur; aortic enlargement by roentgenogram	Dissecting aneurysm of aorta; aortic regurgitation	Rupture of dissecting aneurysm into pericardial sac
Baer, Taussig, and Oppenheimer	1943	14 yr.	Auricular fibrillation. Systolic thrill and murmur over sternum —faint diastolic murmur at base of heart. ECG—PR interval = .20 — .22 sec. (Previous to auricular fibrillation)	Medial degeneration of aorta; coronary ostia abnormally elevated above semilunar valves; mitral valvulitis; Patent foramen ovale	Died suddenly one year after onset of auricular fibrillation
		26 yr.	Angina and congestive failure; systolic and diastolic aortic murmur. ECG—PR interval = .21 sec.	Medial degeneration of aorta; large aortic leaflets; coronary ostia elevated; pulmonary medial degeneration; patent foramen ovale	Sudden death during treatment for congestive failure

in the original aorta and in the aneurysm. Moderate amounts of fibrotic aortic wall structure were seen in the outer wall at the lower end of the aneurysm. There was much acellular necrosis on the inner portions of the aneurysm wall and on the aortic wall itself. Both surfaces were almost completely covered by old unorganized fibrin. In spots there was infiltration of round cells and polymorphonuclear cells together with nuclear debris. The infiltrations found around many of the vasa vasora of the aortic wall, and to a lesser extent the aneurysm wall itself, consisted primarily of macrophages, a few lymphocytes, and an occasional plasma cell. The infiltrations seen in the adventitia consisted primarily of plasma cells. Some of the macrophages were filled with a dark brown hemosiderin-like pigment. The lower end of the aorta showed a little separation of fibers in the inner half of the media; the separation resembled noninflammatory edema. At no place did the microscopic changes suggest syphilis or periarteritis nodosa. The common iliac artery had no marked changes in its media or intima; although there was slight thickening of the latter which suggested early degeneration.

At the apex of the left lung there were numerous tubercles and one area of caseation. The right lung showed slight atelectasis. There was no actual evidence of pneumonia.

Anatomic Summary.—(1) Arachnodactyly, (2) medionecrosis of the aorta, (3) dissecting aneurysm of the aorta with rupture into left pleural cavity, (4) fenestration of the aortic valves, (5) elevation of the coronary ostia, (6) stenosis of the arch of the aorta, (7) ventricular hypertrophy, (8) mitral valvulitis (old), and (9) pulmonary tuberculosis.

DISCUSSION

The case presented demonstrates a dissecting aneurysm and rupture in a young arachnodactylic adult with medionecrosis aortae idiopathica cystica of the type described by Erdheim.⁶¹⁻⁶³ In addition to the medionecrosis, there were present elevation of the coronary ostia above their usual site in the sinuses of Valsalva, fenestration of the aortic valves, and stenosis of the arch of the aorta.

Medionecrosis, elevation of the coronary ostia, aortic insufficiency, and valvular disease were present also in the two cases of Baer, Taussig, and Oppenheimer,⁶⁶ while in the case of Etter and Glover⁵⁷ there was insufficiency of the aortic valve. It is interesting to note that these findings have not been included in previous post-mortem descriptions of younger subjects (Table I).

The question arises as to whether medionecrosis in this case could be explained on the basis of a congenital defect of the aorta which, although not apparent on histologic examination during youth, nevertheless exerted its effect during the period of young adulthood. Schlichter^{64,66} in an analysis of dissecting aneurysm pointed out the role of the vasa vasorum. This finding was confirmed independently by Mote and Carr⁶⁵ who, in their analysis of cases of dissecting aneurysm, noted medionecrosis and suspected hemorrhage of the vasa as a possible starting point in the production of the medial degeneration. Schlichter⁶⁶ demonstrated the occurrence of medionecrosis and dissecting aneurysm in dogs after interference with the vasa vasorum of the aorta. In his experiments the adventitial vasa vasorum of the aorta were cauterized without damage to the medial and intimal structures and later medial degeneration and dissection of the aorta were found.

To explain the appearance of medionecrosis, dissecting aneurysm, and rupture late in the life of the arachnodactylic patient, it is suggested that there may be a developmental anomaly of the nutrient vessels of aorta so that they become progressively less able to nourish the media. Only many future post-

mortem examinations of similar cases will be able to demonstrate the truth or falsity of this suggestion.

That other arteries could be the site of similar lesions was demonstrated by the second case of Baer, Taussig, and Oppenheimer, in whose cases the pulmonary artery showed similar medionecrosis.

Post-mortem examination of future cases should include a demonstration of the vasa vasorum by injection (via the aortic lumen and the coronary arteries) of a radiopaque mass. Radiographic films of the aorta would then exhibit the extent and character of vascularization of the aortic media. Study in a similar manner of the pulmonary and peripheral arterial vascularization would be fruitful.

CONCLUSIONS

1. A case is presented of arachnodactyly with medionecrosis of the aorta, dissecting aneurysm and rupture, elevation of the coronary ostia, aortic stenosis, and mitral valvulitis.
2. A review of previously reported cases with cardiovascular findings is included. Special emphasis has been placed on autopsied cases.
3. A discussion is presented of the late manifestation of medionecrosis involving the great vessels.

REFERENCES

1. Marfan, M. A.: Un cas de déformation congénitale des quatre membrés, plus prononcée aux extrémités, caractérisée par l'allongement des os, avec un certain degré d'amin-cissement, Bull. et mém. Soc. méd. d. hôp. de Paris 13:220, 1896.
2. Poynton, F. C.: Case of Atavism, Tr. M. Soc., London 26:338, 1903.
3. Dubois, M.: Sur un cas de dolichosténomélie, Ann. Soc. méd.-chir. de Liège 12:896, 1912.
4. Salle, V.: Ueber einen Fall von angeborener abnormer Grösse der Extremitäten mit einem an Akromegalia erinnernden Symptomenkomplex, Jahrb. f. Kinderh. 75:540, 1912.
5. Boerger, F.: Ein Fall von Dolichostenomelie (Arachnodactylie), Monatschr. f. Kinderh. 13:335, 1914.
6. Von Pfaundler, M.: Arachnodaktylie, München. med. Wchnschr. 61:280, 1914.
7. Neresheimer, R.: Ueber Arachnodactylie, Arch. f. Kinderh. 65:391, 1916.
8. Poynton, F. J., and Maurice, W. B.: Arachnodactyly With Organic Heart Disease, Tr. M. Soc., London 45:21, 1923.
9. Ormond, A. W., and Williams, R. G.: A Case of Arachnodactyly With Special Reference to Ocular Symptoms, Guy's Hosp. Rep. 74:385, 1924.
10. Piper, R. K., and Irvine-Jones, E.: Archnodactylia and Its Association With Congenital Heart Disease, Am. J. Dis. Child. 31:832, 1926.
11. Schlack, H.: Zur Kenntnis der Arachnodaktylie, Med. Klin. 22:845, 1926.
12. Baessler, F., and Schneider, J.: Zur Kasuistik der Dolichostenomelie, Ztschr. f. d. ges. Anat. (Abt. 2) 13:54, 1927.
13. Moro, Ueber die neurologische Form der Arachnodaktylie, München. med. Wchnschr. 74:1071, 1927.
14. Bier, F.: Ueber einen Fall von Arachnodaktylie, Arch. f. Kinderh. 83:292, 1928.
15. Ormond, A. W.: Etiology of Arachnodactyly, With Special Reference to Ocular Symptoms, Guy's Hosp. Rep. 80:68, 1930.
16. Ingram, W. W., and Inglis, K.: Arachnodactyly Associated With Muscular Hypotonia, M. J. Australia 2:238, 1931.
17. Vogt, A.: Arachnodaktylie (Marfan'scher Symptom komplex) mit totaler Linsenluxation, Ztschr. f. Augenh. 75:388, 1931; Klin. Monatsbl. f. Augenh. 87:258, 1931.

18. Weve, H.: Ueber Arachnodaktylie (Dystrophia Mesodermalis congenita, Typus Marfan), Arch. f. Augenh. 104:1, 1931.
19. Dvork, H. J.: Report of a Case of Arachnodactylie, Proc. Staff Meet., Mayo Clin. 7:715, 1932.
20. Killmna, A.: Zur Kasuistik der Arachnodaktylie, Arch. f. Kinderh. 97:206, 1932.
21. Weill, G.: Extopie des cristallin et malformations générales, Ann. d'ocul. 169:21, 1932.
22. Weber, F. P.: Familial Asthenic Type of Thorax With Congenital Ectopia of Lenses, a Condition Allied to Arachnodactyly, Lancet 2:1472, 1933.
23. Kurz, O.: Einige Fälle von Linsenektomie mit besonderer Berücksichtigung des konstitutionellen Momentes, Klin. Monatsbl. f. Augenh. 92:193, 1934.
24. Villard, H., Viallefont, H., and Temple, J.: Arachnodactylie et subluxation du cristallin. Observation d'une famille, Bull. Soc. d'opht. de Paris, p. 384, 1934.
25. Becker, L.: Linsenektomie in der I., (II.), und III. Generation, Klin. Monatsbl. f. Augenh. 94:547, 1935.
26. Buecklers, M.: Ectopia lentis und Marfanscher Symptomenkomplex, Klin. Monatsbl. f. Augenh. 94:109, 1935.
27. Francois, J.: De la pathogénie et de l'origine hypophysaire du syndrome de Marfan, Bull. et mém. Soc. franc. d'opht. 48:157, 1935.
28. Morard, G.: Arachnodactylie et ectopie bilatérale des cristallines, Arch. d'opht. 52:344, 1935.
29. Passow, A.: Analogie und Koordination von Symptomen der Arachnodactylie und des Status dysraphicus, Klin. Monatsbl. f. Augenh. 94:102, 1935.
30. Puglisi-Duranti, G.: Su i colobomi tipici della corioide e su id colobomi della regione maculare. Coloboma maculare unilaterale e arachnodattilia, Boll. d'ocul. 14:1444, 1935.
31. Burch, F. E.: Association of Ectopia Lentis With Arachnodactyly, Arch. Ophth. 15:645, 1936.
32. Calogero, V. N.: Contributo allo studio della sindrome di Marfan, Boll. d'ocul. 15:847, 1936.
33. Kurz, O.: Irisveränderungen durch Lues bei kongenitaler Ectopia lentis (Beitrag zur Pathologie des Marfanschen Syndromes), Arch. f. Augenh. 109:592, 1936.
34. Lodi, G.: Arachnodactylia, Arch. ital. di pediat. 4:61, 1936.
35. Westendorff, E. G.: Ueber Arachnodaktylie, Kinderärztl. Praxis 7:393, 1936.
36. Charamis, J.: Le syndrome de Marfan, Arch. d'opht. 1:1067, 1937.
37. Fischbach, H.: Beitrag, zur Klinik der Arachnodaktylie und Hinweis auf die Erbllichkeit des Leidens, Ztschr. f. Kinderh. 58:630, 1937.
38. Goedl, H.: Arachnodaktylie mit kongenitalem Uvea-Linsenkolobom, Klin. Monatsbl. f. Augenh. 98:396, 1937.
39. Huber, J., Florand, J., and Lièvre, J. A.: Dolicho Sténomélie, Bull. et mém. Soc. méd. d. hôp. de Paris 53:1473, 1937.
40. Lloyd, R. I.: A Second Group of Cases of Arachnodactyly, Arch. Ophth. 17:66, 1937.
41. Malbrán, J., and Picoli, H. R.: Arachnodactilia (síndrome de Marfan), Arch. de oftal. de Buenos Aires 12:3, 1937.
43. Roch, M.: Arachnodactylie (Syndrome de Marfan), Presse méd. 45:1429, 1937.
43. Apert, E.: Les formes frustes du syndrome dolichosténomélique de Marfan, Nourrisson 26:1, 1938.
44. Cockayne, E. A.: Arachnodactyly With Congenital Heart Disease, Brit. J. Child. Dis. 35:281, 1938.
45. Fitcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med. 61:693, 1938.
46. Giraud, P., Bocca, P., Jayle, G. E., and Mockers: Dolichosténomélie (maladie de Marfan), Bull. Soc. de pédiat. de Paris, 36:713, 1938.
47. Roederer, C.: Un cas d'arachnodactylie, Bull. Soc. de pédiat. de Paris 36:269, 1938.
48. Moore, T.: Arachnodactyly, Arch. Ophth. 21:854, 1939.
49. de Saint-Martin, R.: Clinical Peculiarities of Marfan's Syndrome, Ophthalmologica 98:201, 1939.
50. Norcross, J. R.: Arachnodactylia, J. Bone & Joint Surg. 20:757, 1938.
51. Rambar, A., and Denenhof, E. J.: Arachnodactyly, J. Pediat. 15:844, 1939.
52. Harrison, J., and Klainer, M. J.: Arachnodactyly: Its Occurrence in Several Members of One Family, New England J. Med. 220:621, 1939.

53. Haridas, G.: Arachnodactylia in a Chinese Infant, *Arch. Dis. Childhood* 16:257, 1941.
54. Rados, A.: Arachnodactyly, *Arch. Ophth.* 27:447, 1942.
55. Green, H., and Emerson, P. W.: Arachnodactylia: Clinical Report of Six Cases, *Arch. Pediat.* 60:299, 1943.
56. Baer, R. W., Taussig, H. B., and Oppenheimer, E. H.: Congenital Aneurysmal Dilatation of the Aorta Associated With Arachnodactyly, *Bull. Johns Hopkins Hosp.* 72:309, 1943.
57. Etter, L. E., and Glover, L. P.: Arachnodactyly Complicated by Dislocated Lens, and Death From Rupture of Dissecting Aneurysm of the Aorta, *J. A. M. A.* 123:88, 1943.
58. Bergstrand, C. G.: Arachnodactylia: Pathological Anatomy in Connection With a Case, *Acta Paediat.* 30:345, 1943.
59. Gray, H.: Arachnodactyly, *Arch. Int. Med.* 75:215, 1945.
60. Schneider, W. F.: Arachnodactyly—Unusual Complication Following Skull Injury, *J. Pediat.* 27:583, 1945.
61. Erdheim, J.: Medionecrosis Aortae Idiopathica Cystica, *Virchows Arch. f. path. Anat.* 276:187, 1930.
62. Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, *Am. J. Path.* 8:717, 1932.
63. Roberts, J. T.: Medionecrosis Aortae Idiopathica Cystica, *AM. HEART J.* 18:188, 1939.
64. Schlichter, J.: Beitrag zu den Aneurismen und Rupturen des Herzens, Lausanne, 1940, Univ. of Lausanne Press.
65. Mote, C. D., and Carr, J. L.: Dissecting Aneurysm of the Aorta, *AM. HEART J.* 24:69, 1942.
66. Schlichter, J.: *Arch. Path.* In press.

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS DUE TO ORGANISMS HIGHLY RESISTANT TO PENICILLIN

CASE REPORT

M. GROSSMAN, M.D., D. FELDMAN, M.D., L. N.

KATZ, M.D., AND W. BRAMS, M.D.

CHICAGO, ILL.

IT HAS recently been demonstrated by us¹ and by others that penicillin will cause a clinical arrest of active infection in a great majority of cases of subacute bacterial endocarditis. Treatment failures have arisen as a result of inadequate dosage, too short a period of therapy, or too great an interval between injections when penicillin was administered intermittently during the day. As a result of our own experience a definite plan of therapy was outlined which was successful in fourteen out of seventeen unselected consecutive cases.¹

Another cause for treatment failure arises, as we and others have found, because the infecting organism is very resistant to penicillin. Therapy should not be begun until the sensitivity of the organism to penicillin has been determined. Inasmuch as this insensitivity of the bacterium may often be relative rather than absolute, it would seem possible to effect a cure if higher blood levels of penicillin were attained at the very beginning of treatment. We have used as much as 2,500,000 Oxford units of penicillin per day by continuous injection in our series.¹ Dawson and Hunter² went as high as 500,000 units per day, and rejected three cases because the resistance of the organism to penicillin in vitro was too high. Bloomfield and Halpern³ reported success with 1,000,000 units of penicillin per day in a case having an organism with a penicillin sensitivity of 1.0 Oxford units. Loewe and associates⁴ recently proposed an optimum dosage of 2,000,000 units of penicillin daily for eight weeks in cases with penicillin-resistant organisms.

It seemed to us that higher doses than this might be needed in patients infected with organisms which are unusually resistant to penicillin. In fact, we believe that the penicillin concentration in the blood should be maintained continuously for at least a week, preferably at a level which can be shown to effectively inhibit growth of the infecting organism in vitro, as established by direct test (Schlichter and MacLean,⁵) or four or more times the in vitro sensitivity.

From the Cardiovascular and Medical Departments, Michael Reese Hospital.

Aided by the Herbert G. Mayer Fund for Cardiovascular Research.

The penicillin was supplied by Commercial Solvents, Inc., and the para-aminohippuric acid by Sharpe and Dohme Co.

The department is supported in part by the Michael Reese Research Foundation.

Received for publication Aug. 16, 1946.

A report of the first case treated in this manner follows.

CASE REPORT

R. B., a 17-year-old white boy, was admitted to Michael Reese Hospital on Sept. 22, 1945, for treatment of subacute bacterial endocarditis. At the age of 6 years he had had an attack of rheumatic fever. At the age of 10 years, and again at 13, he had had recurrences of rheumatic fever. Between attacks he had lived a normal, active life. In November, 1944, following a finger laceration, he began to have headaches, fever, and sweating episodes. Numerous petechiae soon appeared. On November 26, he was admitted to another hospital where the diagnoses of rheumatic heart disease with mitral insufficiency and subacute bacterial endocarditis due to *Streptococcus viridans* were made. He was then given eleven days of penicillin therapy, receiving 25,000 units intravenously every two hours. The total amount given was 3,300,000 units. Upon completion of the penicillin course he was put on a maintenance dose of 1.0 Gm. of sulfamerazine every twelve hours. During therapy and for four weeks thereafter, his blood culture remained negative. However, approximately six weeks after completion of therapy his blood cultures again became positive, and a second course of penicillin therapy was given. He received 50,000 Oxford units intravenously every four hours and over a period of twelve days received a total of 3,600,000 units. Following this second course of therapy his cultures remained negative for one month and he was discharged from that hospital. He returned two weeks later because of fever, nausea, generalized abdominal pain, and generalized joint pains. Physical examination at that time revealed a moderate right-sided abdominal tenderness, and positive Murphy punch on the right. Blood cultures were negative, but urinalysis showed numerous white and occasional red blood cells. A diagnosis of "embolic infection of the kidney" was made, and he was put on sulfadiazine. He continued to run a spiking temperature, and after ten days he was transferred to another hospital. At that hospital, blood cultures were again positive for *Streptococcus viridans*. In spite of this he received no therapy for a period of six weeks. He was then given a third course of penicillin consisting of 20,000 units intravenously every two hours for twenty-four days. The total dose was 5,700,000 units. Three weeks after completion of this course his cultures again became positive, and a fourth course was given consisting of 20,000 units of penicillin intravenously every two hours. Over a period of ten days the total amount given was 2,400,000 units. At the end of this fourth course he was discharged, apparently in good condition. Following discharge he continued to administer penicillin to himself, 30,000 to 40,000 units intramuscularly two to three times a day. After six weeks of self-administration he discontinued therapy and within a few weeks all his previous symptoms recurred.

On Sept. 22, 1945, he was admitted to the Michael Reese Hospital. Physical examination showed a thin, chronically ill boy weighing 109 pounds. There were petechiae in the skin, beneath the fingernails, and in the lips. A small, recent, superficial retinal hemorrhage was seen in the left fundus. The lungs were clear to percussion and auscultation. A systolic thrill was felt over the apex of the heart. There was no cardiac enlargement on percussion. There was a harsh, low-pitched systolic murmur over the apex transmitted to the axilla. The first sound over the apex was accentuated; the second pulmonic sound was slightly louder than the aortic sound. The spleen was felt three finger-breadths below the left costal margin. Numerous small, red, slightly tender macular and nodular lesions about 1 to 3 mm. in diameter were present on both palms.

Laboratory data revealed 3,860,000 red blood cells and 7,250 white blood cells per cubic millimeter. Hemoglobin was 12.5 grams. The differential blood count was normal. The sedimentation rate was 37 mm. in one hour (Landau method, normal under 18 mm. in one hour). Urinalysis showed a 2 plus albumin, 2 to 3 red blood cells per high power field, and occasional granular casts. Blood nonprotein nitrogen was 44 mg. per 100 c.c.; and blood glucose, 92 mg. per 100 cubic centimeters. The Wassermann and Kahn tests were negative. Teleroentgenogram showed the lungs to be clear and the heart of normal size. Fluoroscopy revealed a slight posterior enlargement of the left atrium. In the electrocardiogram there were small T waves in the limb leads and notching of the T in Leads II and CFs. Numerous blood cultures, some taken after the administration of adrenalin, were positive for *Streptococcus viridans*. Several sensi-

tivity tests indicated that this organism was inhibited by 5.0 Oxford units of penicillin per cubic centimeter.*

The diagnoses made were rheumatic heart disease with mitral stenosis and insufficiency and subacute bacterial endocarditis (*Streptococcus viridans*).

During the period in which these studies were being made, he ran a spiking temperature which varied between 102° F. and 98.6° F. rectally. On Oct. 3, 1945, a course of penicillin therapy was begun. Three million units in 2,000 c.c. of 5 per cent glucose (in distilled water) were given by continuous intravenous drip every twenty-four hours. This was continued for thirty-five days, when, because of a temporary shortage of penicillin, the dose was reduced to 1,000,000 units for one day. For the next seven days he was given 6,000,000 units per day. Concurrently with this increase in the penicillin dosage, the sodium salt of para-aminohippuric acid was administered intravenously in 2.5 per cent solution. This was administered continuously in the same solution with the penicillin, and was continued for five consecutive days. The total dose in these five days was 250 Gm., or 50 Gm. daily.

Shortly after the course of penicillin was begun the patient's temperature slowly fell to normal and remained there. Weekly blood cultures were negative except for one during the third week of therapy, which yielded a few gram-positive cocci which, however, failed to grow in subcultures, and was eventually reported as negative. Blood and differential counts remained essentially the same throughout the course of treatment. The sedimentation rate fell gradually from 37 mm. in one hour to 20 mm. in one hour. Urinalyses showed a gradual decrease in albumin, cells, and casts. A weight gain of 13 pounds was recorded during the treatment.

Penicillin blood levels rose slowly until on the ninth day of therapy the level was 10 Oxford units per cubic centimeter.† It remained at that approximate level until the thirty-fourth day of treatment when it dropped to 3.2 Oxford units per cubic centimeter. Shortly thereafter, with penicillin dosage increased to 6,000,000 units per day and with the added para-aminohippuric acid, the level rose to 20 Oxford units per cubic centimeter. The plasma para-aminohippuric acid level⁸ at that time was 4.65 mg. per cent. By the fifth day of this combined therapy the penicillin level was 41 Oxford units per c.c. and the para-aminohippuric acid level 18 mg. per cent. Two days after the para-aminohippuric acid was discontinued but while the patient was still receiving 6,000,000 units of penicillin, the level had dropped to 6.4 Oxford units per cubic centimeter.

The patient's condition remained good throughout the course of therapy. Except for superficial thromboses of the veins at the sites of venepuncture, there were no complications until the final day of therapy. At that time he began to complain of right-sided abdominal pain and nausea, and his temperature rose to 100° Fahrenheit. White blood count was 8,250 per c.mm., and urinalysis was negative. Murphy punch was negative. A diagnosis of acute appendicitis was made, and this was confirmed at operation the same day. He was then continued on 1,500,000 units of penicillin per day for two additional days. The postoperative course was smooth. There was no temperature elevation. He was out of bed in three days and walking in five days. His cardiac status remained unchanged throughout the course of therapy and the operation.

Following cessation of penicillin therapy, he continued to feel well. Blood cultures remained negative. Temperature, urinalyses, blood counts, and sedimentation rates continued normal. Weight gain was consistent, being 133 pounds on discharge as compared with 109 pounds on admission. He was discharged on December 14, his eighty-fourth hospital day.

Following his discharge from the hospital he felt well. He remained afebrile and continued to gain weight. Frequent blood cultures were negative except for one on Dec. 20, 1945. This yielded in one of six flasks a slow-growing gram-positive streptococcus differing from his original organism in cultural characteristics and penicillin sensitivity. Subsequent cultures, however, have remained negative. It was felt that this single positive blood culture possibly represented a transient bacteremia, the source of which was probably carious teeth. Therefore, he was readmitted to Michael Reese Hospital on Jan. 7, 1946, for extraction of those teeth.

*Modification of Fleming's titration method.⁶

†Modification of Rammelkamp's titration method.⁷

On this admission the physical findings were essentially as on the previous discharge. The red blood count was 4,850,000, with 15.5 Gm. hemoglobin. White blood count was 8,500 with a normal differential count. Sedimentation rate was 16 mm. in one hour.

On Jan. 12, 1946, he was started on a daily dose of 6,000,000 units of penicillin given by continuous intravenous drip. A penicillin level of 5.2 Oxford units per c.c. was reached. On January 15, four teeth, in which the pulp cavity was involved by caries, were extracted. The alveolar sockets were packed with penicillin impregnated gauze.¹ He continued to receive 12,000,000 units of penicillin intravenously over the first fifty hours following the extractions. There was a mild temperature elevation for two days following the extractions (which was not unexpected), but otherwise the course was uncomplicated.

Since his discharge, repeated cultures have been negative, and he has been afebrile and clinically well. The subacute bacterial endocarditis, therefore, has been arrested for twenty-one and one-half months to Aug. 1, 1947.

Fig. 1 is a graph representing the pertinent data of his first hospital stay under our care.

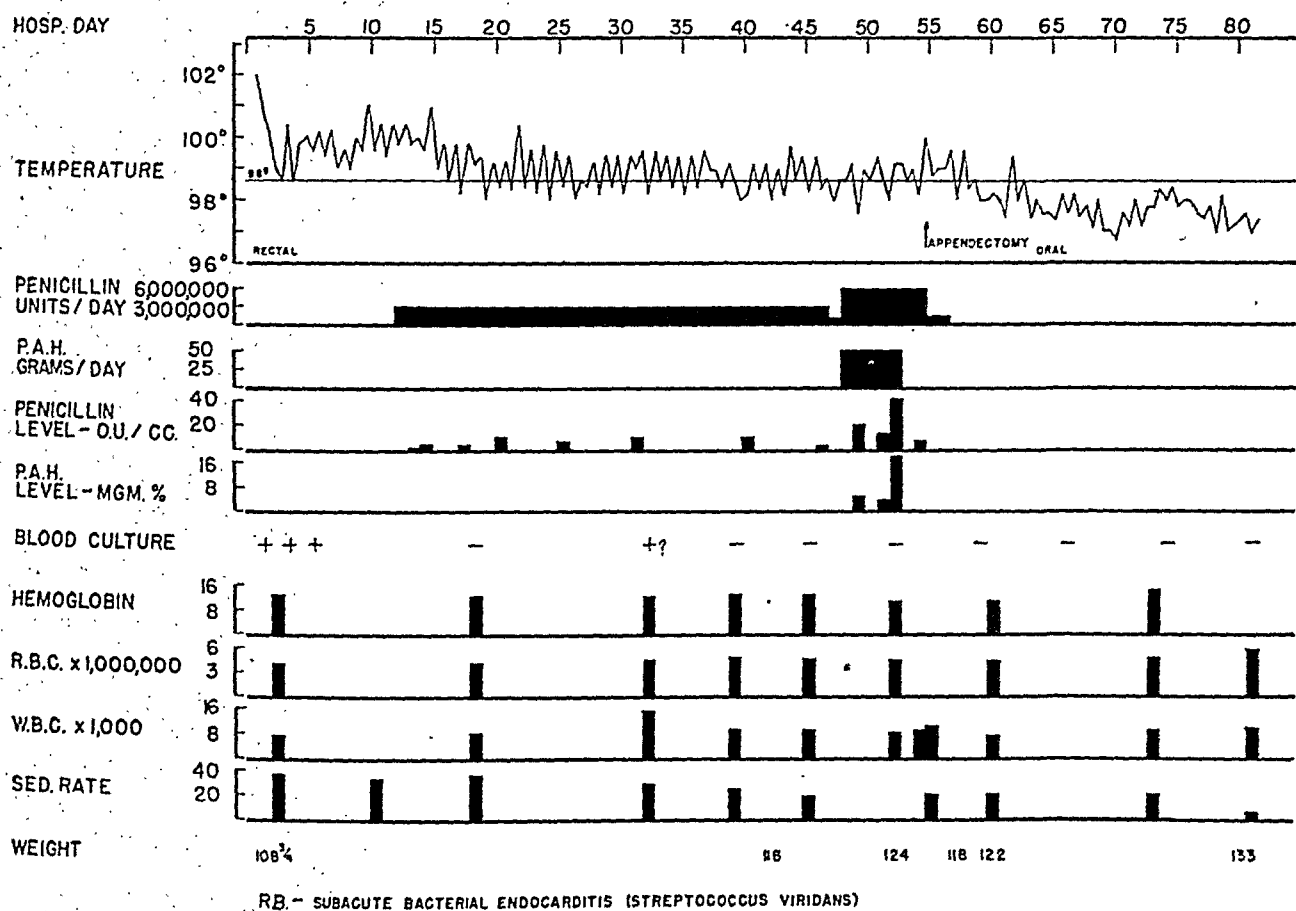


Fig. 1.—Summary of the clinical features and treatment.

DISCUSSION

It is generally agreed that the two primary prerequisites for penicillin treatment of subacute bacterial endocarditis are: (1) continuous maintenance of an adequately high blood penicillin level, and (2) sufficiently prolonged treatment. The adequacy of the blood level cannot be judged from the dosage required to clear the circulating blood of organisms. This latter can be accomplished with inadequate doses⁹ but under such circumstances recurrences usually occur within a month after penicillin is discontinued. It has been assumed that in-

adequate dosage not only fails to cure but that actually such a regimen may make the organism more resistant. Thus, Flippin and associates¹⁰ report a case in which the *in vitro* sensitivity of the organism rose after inadequate penicillin therapy from 0.025 to 0.75 Oxford units per cubic centimeter. Such an apparent increase in organism resistance to penicillin may be due actually to the presence originally of organisms of varying penicillin resistance. The inadequate penicillin dosage may under such circumstances inhibit the less resistant organisms and permit the more resistant ones to multiply without competition. Demerec¹¹ has expressed this view in connection with the development of resistance in organisms exposed to penicillin *in vitro*. If this viewpoint is correct, it follows that it is unwise to treat cases with inadequate doses of penicillin. Further, improperly treated cases will require more intense and more prolonged subsequent therapy than is usually given.

There are as yet insufficient data to define precisely what constitutes minimum duration of therapy and a minimum necessary blood penicillin level. It is our impression that ordinarily for organisms of average resistance to penicillin six weeks of continuous treatment is necessary to ensure penetration of the vegetations by penicillin to inhibit the organism located there. As to the penicillin blood level, this should be kept at least up to three or four times the *in vitro* sensitivity of the organism for a week or more.⁵

In the case reported, it appears that the blood stream was cleared of bacteria after a few days of penicillin therapy. The single subsequent questionably positive culture obtained after three weeks of therapy may have been due to the breaking off of a friable vegetation. With the administration of 3,000,000 units per day a level of 10 Oxford units per c.c. of blood was obtained. Subsequently, however, the penicillin blood level fell, presumably as the kidney function improved. For this reason the dosage was increased to 6,000,000 units per day, and in addition, para-aminohippuric acid was given for five days. With this combination a blood level of 20 to 40 Oxford units per c.c. was attained; the latter value approached closely the maximum level hitherto obtained. Dawson and Hunter¹⁴ achieved as high as 51.2 Oxford units with 10,000,000 units of penicillin.

Loewe and co-workers¹² have estimated that with continuous intravenous administration of penicillin a blood level will be reached of approximately one unit for each 1,000,000 units given per day; thus, they obtained a maximum level of 9.2 Oxford units per c.c. with a daily dose of 10 million units. Loewe and associates¹³ have also reported that the administration of para-aminohippuric acid in quantities sufficient to give a plasma hippurate level of over 10 mg. per cent usually results in a three- to sixfold elevation of blood penicillin level. Levels of hippurate below 10 mg. per 100 c.c. in the blood were reported to be without effect on the penicillin level. The results in our case are at variance with those of Loewe and associates. The blood level of penicillin attained per million units of penicillin administered per day was about 3 units per c.c., and plasma levels of para-aminohippuric acid of 3 to 5 mg. per 100 c.c. caused a demonstrable raising of the penicillin blood level. The differences in effect in our case are undoubtedly due to the impairment of renal tubular function.

The massive doses of penicillin used in our case were without untoward effect. Likewise, the continuous administration of para-aminohippuric acid for five days did not lead to any toxic manifestations. There were no alterations produced in urinary output, blood nonprotein nitrogen, and in the measured urinary constituents.

It is of interest that appendicitis can occur during administration of such large doses of penicillin therapy. Surgery was carried out successfully and did not affect the course of the subacute bacterial endocarditis.

CONCLUSION

The satisfactory results obtained in this case demonstrate that a regimen of intensive penicillin therapy may in certain cases of subacute bacterial endocarditis with resistant organisms convert treatment failures into treatment successes.

ADDENDUM

It may be of interest to report the present status of the first seventeen patients we treated with penicillin, since there is need of long-term follow-up on such cases. On March 1, 1946,¹ we reported that three patients had died during or just after treatment, and that fourteen were alive from eight to twenty months after penicillin therapy had been stopped. Of these living patients, four had varying degrees of congestive heart failure and two had recurring petechiae. One of the surviving patients died in congestive failure eight months after penicillin therapy had been stopped.

Between March, 1946, and August, 1947, one more patient died in congestive failure nine months after penicillin therapy had been stopped. The total deaths, therefore, as of August, 1947, are five, with the remaining twelve patients surviving for periods of from twenty-eight to thirty-six months (a long-term survival rate of 70.6 per cent). Of the twelve surviving patients, four have had varying degrees of congestive heart failure; one developed it in the interim between reports during the seventh month of her pregnancy. A cesarean section was done; the baby died but the patient survived, and has been symptom free to date. One, who was in mild failure during therapy and for a number of months thereafter, is now symptom free without medication. Two have continued to have congestive failure. Two patients have had continued petechiae, and one developed an equivocal recurrence of the infection (repeated negative blood cultures) ten months ago, twenty-one months after the initial penicillin therapy had been stopped. Another course of penicillin was given to this patient. She is now well except for mild heart failure.

Of the twelve who are now living, eleven are carrying on full activity; the other case is one of a progressively incapacitating congestive failure.

We are indebted to Dr. J. G. Schlichter for assistance in the management of this case. We are also indebted to Miss H. MacLean of the Department of Bacteriology for the cultural and penicillin determinations, and to Mrs. Lillian Havel for determining the para-aminohippuric acid blood levels.

REFERENCES

1. Mokotoff, R., Brams, W., Katz, L. N., and Howell, K.: Treatment of Subacute Bacterial Endocarditis With Penicillin. Results of 17 Consecutive Unselected Cases, *Am. J. M. Sc.* 211:395, 1946.
2. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin. Results of 20 Cases, *J. A. M. A.* 127:129, 1945.
3. Bloomfield, A., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* 129:1135, 1945.
4. Loewe, L., Plummer, M., Niven, C. F., and Sherman, J. M.: Streptococcus s.b.e. in Subacute Bacterial Endocarditis, *J. A. M. A.* 130:257, 1946.
5. Schlichter, J. G., and MacLean, H.: A Method of Determining the Effective Therapeutic Level in the Treatment of Subacute Bacterial Endocarditis With Penicillin. A Preliminary Report, *AM. HEART J.* In press.
6. Fleming, A.: In-Vitro Tests of Penicillin Potency, *Lancet* 1:732, 1942.
7. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, *Proc. Soc. Exper. Biol. & Med.* 51:95, 1942.
8. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, 1944, Commonwealth Fund, p. 203.
9. Keefer, C. S.: Penicillin. Its Present Status in the Treatment of Infections, *Am. J. M. Sc.* 210:147, 1945.
10. Flippin, H. F., Mayock, R. L., Murphy, F. D., and Wolferth, C. C.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* 129:841, 1945.
11. Demerec, M.: Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin, *Proc. Nat. Acad. Sc.* 31:16, 1945.
12. Loewe, L., Rosenblatt, P., Russell, M., and Altire-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual Serum Levels of Penicillin. Comparative Studies With Particular Reference to Fractional and Continuous Intramuscular Administration, *J. Lab. & Clin. Med.* 30:730, 1945.
13. Loewe, L., Rosenblatt, P., Altire-Werber, E., and Kozak, M.: The Prolonging Action of Penicillin by Para-Aminohippuric Acid. Preliminary Report, *Proc. Soc. Exper. Biol. & Med.* 58:298, 1945.
14. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin, Second Report, *Ann. Int. Med.* 24:170, 1946.

RETICULUM CELL SARCOMA WITH CARDIAC METASTASIS

REPORT OF TWO CASES WITH ANTE-MORTEM DIAGNOSIS OF ONE

IRVING B. BRICK, M.D.,* BOSTON, MASS., AND CAPTAIN MAURICE GREENFIELD,†
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE following report is based on a study of two cases of reticulum cell sarcoma, both of which were referred to the radiation therapy center at Walter Reed General Hospital for treatment of gastric neoplasm during the past year. Both cases presented an extremely interesting spread of the disease and showed other unusual features. One of the cases represents what we believe is primary reticulum cell sarcoma of the stomach (Case 2) which in itself is a rare entity. In addition, metastatic involvement of the heart was found in both cases, and in one patient (Case 1) was diagnosed during life.

At the time of Yater's¹ stimulating report on tumors of the heart and pericardium in 1931, cardiac involvement, both primary and secondary, was considered rare. Approximately six cases had been described and diagnosed ante mortem. In the fifteen years that have elapsed, fifteen additional cases have been diagnosed ante mortem and reported. The present report adds another. It is our belief that Yater's¹ emphasis upon certain aspects of the symptomatology stimulated the attempt to diagnose these cases during life. Yater felt that secondary cardiac tumors were more common than the primary type, but an approximate compilation of tumors of the heart reported in the literature since 1918 by Lisa, Hirschhorn, and Hart² did not support this view. They listed forty-one cases of primary benign tumor, thirty-one cases of malignant tumor, and forty-seven cases of metastatic tumor of the heart. It is quite interesting to note that many of the cases listed were reported subsequent to Yater's¹ article. However, in large series of autopsy material, as will be shown from a review of the literature, metastatic tumors predominate.

Of the twenty cases of cardiac tumors diagnosed clinically and confirmed by autopsy, listed in the article by Doane and Pressman,³ three had primary tumors of the heart and the remaining seventeen showed metastatic involvement. To complete the list to date, one might add the case of fibromyxosarcoma, a primary tumor, reported by Ravid and Sachs,⁴ and one of the cases to be presented in this paper. This makes a current total of twenty-two cases of

From the Gastriontestinal and Radiology sections, Walter Reed General Hospital, Washington, D. C.

Received for publication Oct. 4, 1946.

*Fifth and Sixth Medical Services (Boston University), Boston City Hospital.

†Walter Reed General Hospital, Washington, D. C.

tumor of the heart diagnosed ante mortem and reported in the literature. In four of these the tumors were primary.

In the résumé of cases by Lisa and colleagues,² Zemansky's⁵ case of a spindle cell sarcoma of the epicardium was not included. To complete Lisa's list, the following cases of metastatic cardiac tumors should be added: A case of reticulum cell sarcoma of the nose reported by Hsiung, Szutu, Hsieh, and Lieu;⁶ a case of myoblastoma of the frontal bone reported by Shelburne and Aronson;⁷ a case of bronchogenic carcinoma reported by Reuling and Razinsky;⁸ a case of adenoacanthoma of the cervix reported by Doane and Pressman.³ Greiner⁹ and Cabot Case Records, Case Number 27281¹⁰ each reported a case of reticulum cell sarcoma which involved the heart, but the discovery of the tumor was a post-mortem finding. Rosenbaum, Johnston, and Alzamora¹¹ reported a case of carcinoma of the esophagus with massive metastases to the heart. Two additional cases of primary cardiac tumors have been reported by Hamilton-Paterson and Castleden.¹²

In Yater's¹ article, various autopsy series were reviewed. Since then, several other series have been reported. Lymburner¹³ found four primary and fifty-two secondary tumors of the heart in 8,500 autopsies at the Mayo Clinic. Pollia and Gogol,¹⁴ in reviewing 12,000 autopsies which included 1,450 cases of malignant tumors, found twenty-nine cases of metastatic cardiac tumors. Helwig¹⁵ reported nine cases of tumors of the heart in 1,000 autopsies. Burke¹⁶ listed fourteen metastatic tumors of the heart in 327 cases of malignancy. Willis,¹⁷ in 332 autopsies on malignant tumors, found metastatic lesions of the heart in twenty cases. Scott and Garvin,¹⁸ in 1,082 cases of malignant disease in a series of 11,100 consecutive autopsies at the Cleveland City Hospital, found the heart or parietal pericardium, or both, to be involved in 118 cases, an incidence of 10.9 per cent of the 1,082 cases of malignant disease. The detailed analysis of their series is interesting as the authors found that carcinoma of the bronchus and breast accounted for 48 per cent of the metastatic cardiac lesions. Nine cases of reticulum cell sarcoma are listed, in six of which cases there was myocardial metastasis. In thirteen cases of lymphosarcoma, only one case revealed myocardial metastasis. The infrequency of carcinoma of the stomach metastasizing to the heart is indicated by the presence of but one myocardial and one pericardial metastasis in 201 cases of gastric carcinoma. In reviewing the clinical records, Scott and Garvin¹⁸ found that myocardial insufficiency developing in a patient without other apparent cause but with a malignant disease is an important sign suggestive of cardiac metastasis. Heart block was not observed. In only one case in this extensive series was the diagnosis made ante mortem.

Ritchie,¹⁹ in reviewing 3,000 autopsies, found sixteen cases of metastatic tumor of the myocardium. In these, thirteen different primary sources were recorded. This is in agreement with Yater's¹ opinion of the varied sources of primary tumor. In no case was a clinical diagnosis made.

In a series of 4,050 autopsies made at the Jefferson Hospital, Philadelphia, Herbut and Maisel²⁰ found 640 cases of cancer. In thirty-five cases the heart was secondarily involved. The frequency of cardiac involvement in various autopsy series varies from 0.03 to 1.4 per cent of the total number of autopsies

and from 1.0 to 10.9 per cent of the total number of cancers. In this series, lymphosarcoma was noted in sixteen cases, in three of which there was cardiac metastasis. No reticulum cell sarcomas were recorded. In none of the cases was cardiac metastasis diagnosed before death.

Search of the literature shows that reports of reticulum cell sarcoma with cardiac metastasis have been made infrequently. Fishberg's²¹ case of reticulum cell sarcoma with cardiac metastatic lesions was diagnosed ante mortem. A reticulum cell sarcoma of the nasal cavity with metastatic involvement was reported by Hsiung and associates.⁶ This was also diagnosed ante mortem. Additionally, the cases of Greiner⁹ and Cabot Case Records, Case Number 27,281¹⁰ also showed reticulum cell sarcoma involving the heart. Scott and Garvin¹⁸ listed six cases of cardiac metastasis from reticulum cell sarcoma. In all, ten cases of reticulum cell sarcoma with cardiac involvement have been previously reported. Two of these cases were diagnosed ante mortem.

CASE REPORTS

CASE 1.—The patient was a 25-year-old Italian prisoner of war who was in good health until July, 1944, when he noticed swelling of the glands under his right ear. A month later the inguinal nodes became swollen and he was admitted to the hospital where an operation for a left varicocele was performed. The postoperative course was uneventful, but he was readmitted to the Regional Hospital at Fort Bragg, N. C., on Oct. 19, 1944, because of generalized peripheral lymphadenopathy. A biopsy of an inguinal lymph node was made and reported to show reticulum cell sarcoma, a diagnosis which was later confirmed by the Army Institute of Pathology. The patient was transferred to Lawson General Hospital for treatment on Nov. 21, 1944.

On admission, examination revealed bilateral enlargement of the cervical lymph glands, the largest of which measured about 2 cm. in diameter. Shotty nodes were present in both inguinal and axillary regions. Examination of the abdomen at that time was negative. The patient did not appear ill on admission and remained ambulatory and afebrile during his stay in the hospital. He was treated with roentgen therapy. From Jan. 1, 1945, to Jan. 12, 1945, he received a dose of 1200 roentgens (air) to each axilla through a 10 × 10 cm. portal, and 800 roentgens (air) to each cervical area through a 10 × 15 cm. portal. The following physical factors were employed: 220; 15; 1 mm. copper, 1 mm. aluminum filtration; 50 cm. target-skin distance; 42 roentgens per minute. The peripheral nodes rapidly diminished in size. The patient was discharged from Lawson General Hospital on Feb. 11, 1945, and returned to duty.

In August, 1945, the patient began to have recurrent epigastric pain which was relieved by food. One month later, at Fort Bragg, N. C., he had an x-ray examination of the gastrointestinal tract which apparently revealed no organic lesion. For the first few weeks the pain was moderate in intensity but soon became very severe. It was not associated with nausea or vomiting and it occurred only during the day. Later, the pain occurred at night and became severe enough to awaken him from sleep. In the latter part of September, 1945, the patient began to vomit, sometimes after meals. In the first week of October, 1945, he was sent to New York for repatriation to Italy and boarded the vessel at the port of embarkation. Increasing pain and hematemesis led to his being transferred from the ship to the Station Hospital, Staten Island, N. Y. He was given two transfusions of whole blood and treated as a case with bleeding peptic ulcer. Because the patient did not improve under treatment, he was transferred to the Regional Hospital, Fort Jay, N. Y., on Nov. 16, 1945.

On admission to the hospital he appeared anemic and showed evidence of recent weight loss. A month later, examination of the abdomen revealed a firm mass in the left epigastrium, four finger-breadths below the left costal margin. In December, radiographic examination showed a large filling defect in the fundus of the stomach and the patient was transferred to Walter Reed General Hospital on Jan. 10, 1946, with diagnosis of gastric neoplasm, type undetermined.

On admission he complained of severe "burning pain" in the upper part of the abdomen which radiated to the lower dorsal region, and was accompanied by nausea and occasional vomiting.

He weighed about 120 pounds, having lost 45 pounds in the previous four months. Physical examination revealed a chronically ill, anemic man who had palpably enlarged posterior cervical, bilateral axillary, and bilateral inguinal nodes. The liver was palpable 3 cm. below the right costal margin and was tender. In the left epigastrium a mass could be felt which was hard and moved slightly on respiration. The heart and lungs were normal. Radiographic examination of stomach (Fig. 1) on Jan. 17, 1946, revealed enlargement of the liver and massive rounded filling defects throughout the stomach; these were more marked in the pyloric end. The roentgenologic diagnosis was carcinoma of the stomach. A gastric analysis was within normal limits. An axillary gland was removed for biopsy and the pathologic report, although inconclusive, stated that the appearance was "consistent with early Hodgkin's disease."

Laparotomy was performed Jan. 25, 1946. The stomach was found to be fixed to the under surface of the liver, and could not be delivered into the operative incision. Palpation revealed a soft indurative process in the pylorus. A large ulcerated area could be felt. About midway up the lesser curvature of the stomach the infiltration seemed to extend into the left lobe of the liver where there was a mass the size of a tennis ball. There were many small nodules in the gastrohepatic omentum and much larger ones grouped about the superior mesenteric vessels. Because of the extent of the neoplastic process, resection was not feasible. Several glands were removed from the gastrocolic omentum for biopsy and exhibited "early transformation into lymphosarcoma, probably reticulum cell type."

About three days after operation the patient began to vomit blood. From February 1 to February 20 he received twenty-five transfusions, 500 c.c. each, of whole blood. All food by mouth was withheld and he received morphine and amigen. Occasional vomiting of coffee-ground material occurred, but by February 24 there was slight improvement. He was able to sit up in bed and take a diet of clear liquids. His hematocrit on February 20 was 33 with a red cell count of 3,400,000.

X-ray therapy was begun on Feb. 8, 1946, and from then until March 8, 1946, he received a dose of 3,300 roentgens to the anterior abdomen and 1,800 roentgens to the posterior abdomen. The size of the treatment portals was 15×20 cm. and directed so as to crossfire the epigastric mass. The doses were measured in air with back scatter and a tissue dose of 3,162 roentgens was delivered into the stomach. The following physical factors were employed: 1,000; 3M; 70 cm. target-skin distance; 3 mm. Tungsten filter; half-valve layer = 3.6 mm. lead; 88 roentgens per minute.

There was moderate improvement under radiation treatment and by March 18, 1946, the patient was largely asymptomatic and was able to take small frequent feedings. He was ambulatory and had gained about three pounds in weight.

On March 4, 1946, five days prior to the completion of roentgen therapy, x-ray examination revealed some shrinkage in the size of the mass previously noted in the stomach. In the following week the patient's condition became worse and he was unable to eat solid food without vomiting. By April 6, 1946, x-ray examination revealed complete obstruction at the pyloric end of the stomach. In nine days the hematocrit dropped from 40 to 31 and for the first time subcutaneous nodules were noted on the anterior abdominal and anterior chest wall. Some of the nodules were as large as a cherry. One was removed for histologic examination, and a diagnosis of reticulum cell sarcoma was made.

In the next two weeks the patient's condition deteriorated progressively. He was severely nauseated and unable even to take fluid by mouth without vomiting. The vomitus consisted of bile-tinged fluid. Treatment consisted of intravenous amigen and glucose.

On April 14, 1946, the patient began to complain of shortness of breath. Examination of the heart revealed a ventricular rate of 60 per minute and what appeared to be a protodiastolic gallop at the apex. There was no pericardial friction rub. Râles were heard at both lung bases. A presumptive diagnosis of metastasis to the heart was made. An electrocardiograph (Fig. 2) made on April 14 showed complete A-V heart block, with an auricular rate of 100 and a ventricular rate of 46 per minute. Low voltage was present in the limb leads. A second electrocardiogram

BRICK AND GREENFIELD: SARCOMA WITH CARDIAC METASTASIS

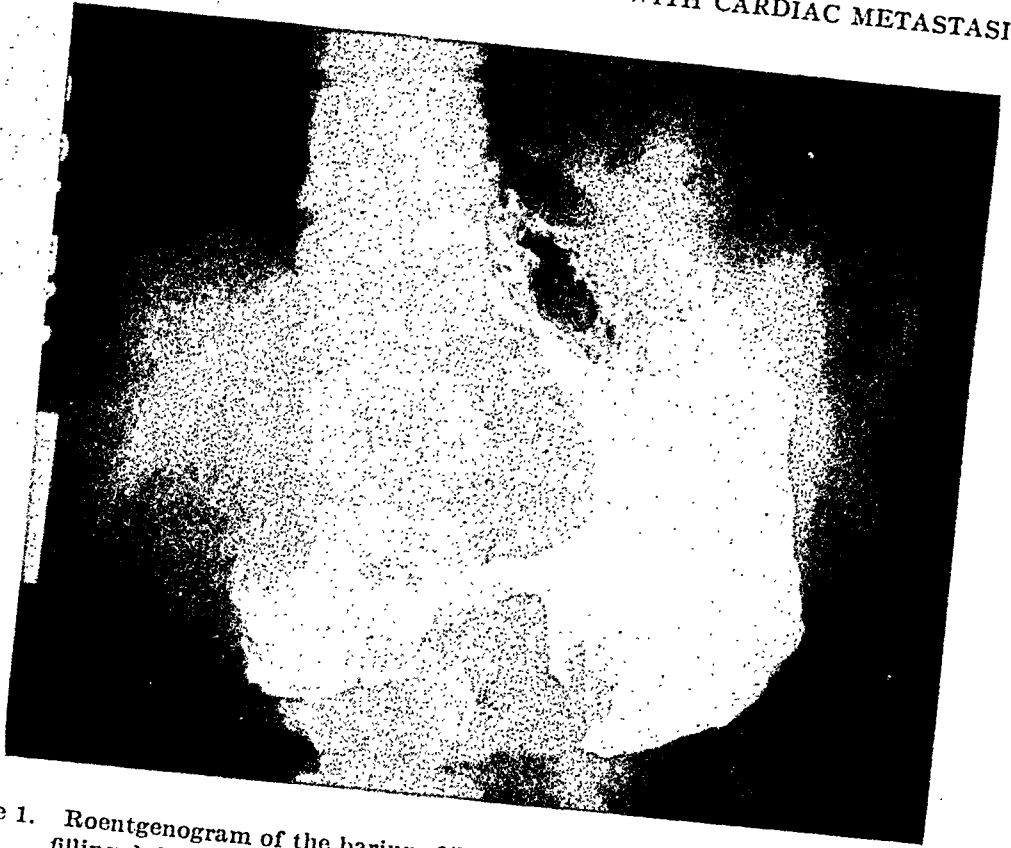


Fig. 1.—Case 1. Roentgenogram of the barium-filled stomach made on Jan. 17, 1946, showing a huge filling defect in the antrum of the stomach on the greater curvature.

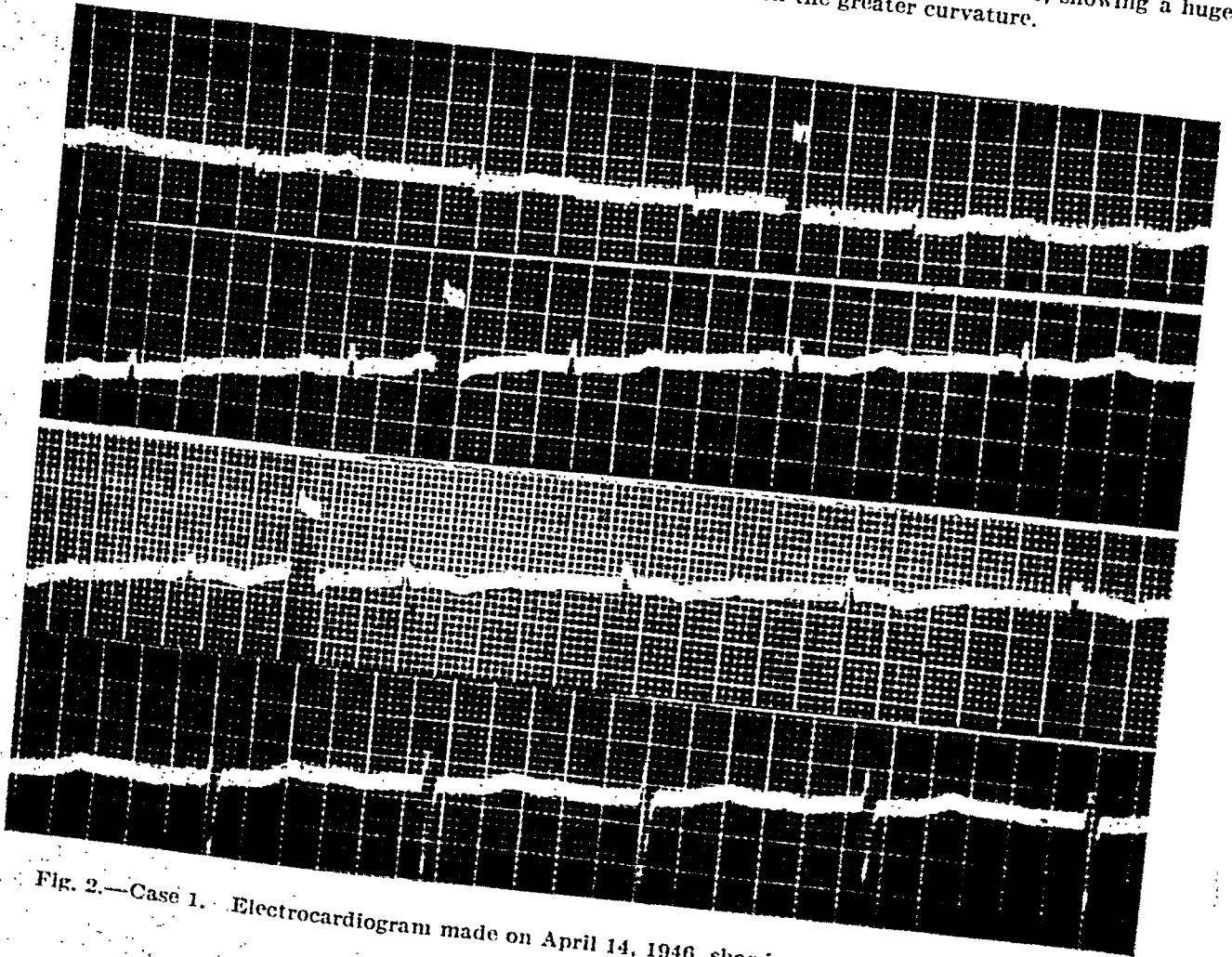


Fig. 2.—Case 1. Electrocardiogram made on April 14, 1946, showing complete A-V heart block.

three days later was essentially similar. A roentgenogram of the chest (Fig. 3) showed marked cardiac enlargement. In view of the radiographic and electrocardiographic findings and because of the widespread subcutaneous metastases, the diagnosis of myocardial metastasis was considered to be confirmed.

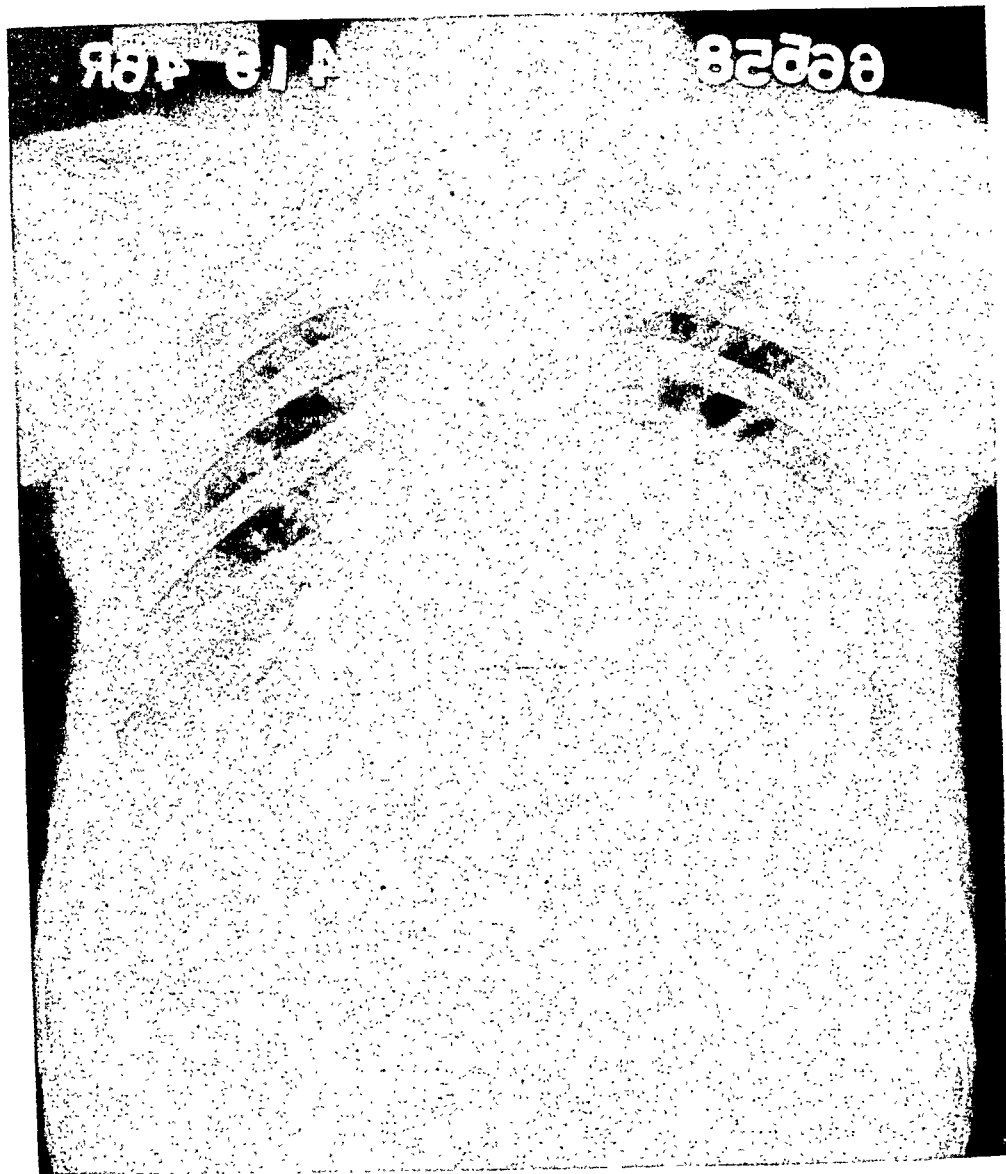


Fig. 3.—Case 1. X-ray film of the chest made on April 19, 1946, showing marked increase in size of the cardiac shadow and suggesting pericardial effusion and cardiac dilatation.

The patient continued to complain of shortness of breath and on April 17, 1946, cyanosis of the lips was noted. Three days later, he suddenly complained of severe pain in the stomach. On examination he was seen to be cyanotic, cold, and clammy. The pulse could not be felt. The heart rate was 30 per minute. The rhythm was irregular. He soon became unconscious, the heart sounds became inaudible, and breathing was irregular. He expired after several minutes.

The clinical diagnosis was reticulum cell sarcoma involving stomach, heart, lymph nodes, liver, and subcutaneous tissues.

Post-Mortem Examination: The peritoneal cavity contained approximately 5,000 c.c. of clear amber fluid. Numerous adhesions were present between the omentum and transverse colon, and firm adhesions were present between the superior surface of the left lobe of the liver and dome of the diaphragm. There was a large 5 cm. mass of very firm, homogeneous white tissue in the region of the porta hepatis and the pylorus. The mass surrounded the inferior vena cava in this region. The mesentery contained numerous lymph nodes which varied in size from 1 to 3 cm. in diameter. They were oval, very firm, and on section were found to be made of a homogeneous pink, pale tissue. The centers of the larger nodes showed necrosis.

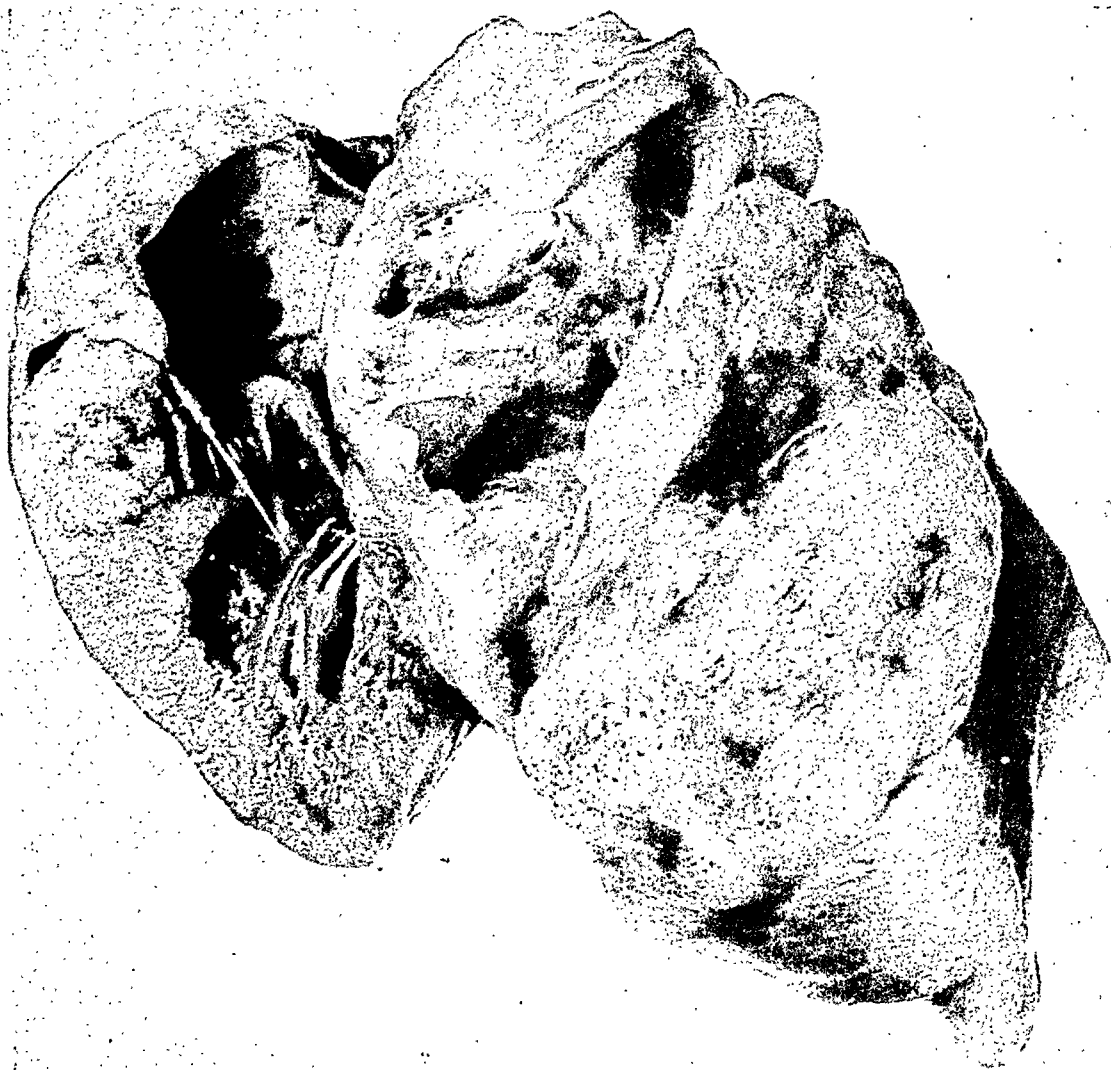


Fig. 4A.—Case 1. Post-mortem photograph of the heart showing massive nodular infiltration of firm gray tumor tissue in the left atrium and both ventricles.

Each pleural cavity contained about 1,000 c.c. of clear, straw-colored fluid. Many fibrinous adhesions were present between the visceral and parietal pleura on both sides. The left lung weighed 330 grams and the right lung 370 grams. Both lungs were moderately collapsed but crepitant throughout. On section, no tumor nodules were seen.

The pericardial cavity contained 500 c.c. of clear straw-colored fluid, and numerous adhesions were present between the visceral and parietal pericardium. The heart (Fig. 4A) weighed 465 grams. There was firm gray tissue invading the entire wall in the region of the atrioventricular septum and extending about 2 cm. into the lower portions of the auricles and upper portions of the ventricles. The neoplastic infiltration extended inferiorly into the anterior wall of the right ventricle for a distance of 5 centimeters. The epicardium over the tumor tissue was rough and

granular. There was invasion of the root of the aorta, pulmonary artery, and superior vena cava. Section of the myocardium showed yellowish-white tissue completely replacing the cardiac muscle. No abnormalities of the valves or coronary vessels were seen. Microscopic examination of sections from the heart (Fig. 4B) showed massive infiltration of the myocardium with reticulum cell sarcoma.

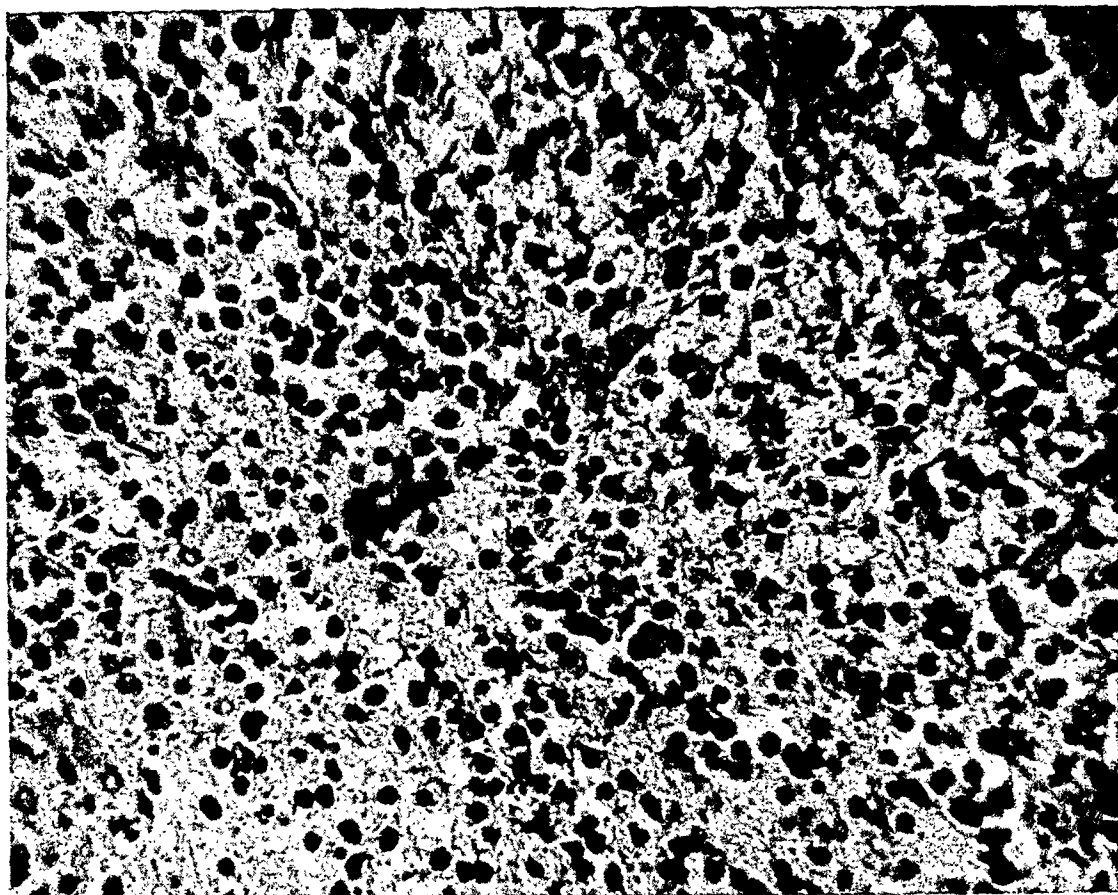


Fig. 4B.—Case 1. Photomicrograph (x440) of section from the heart showing diffuse infiltration with reticulum cell sarcoma.

The spleen weighed 225 grams, and on section the cut surface was dark red and the tissue firm. The liver weighed 2,890 grams. Section of the left lobe showed almost complete replacement by firm yellow tumor tissue in which faint outlines of the liver lobules were seen. The medial half of the right lobe showed similar massive invasion by tumor extending from the left lobe. The lower portion of the esophagus at the hiatus was surrounded by firm white tumor tissue. The stomach was dilated and contained about 1,000 c.c. of cloudy watery fluid. The wall of the stomach was irregularly thickened by firm white homogeneous tumor tissue. The mucosa of the stomach was thickened, and in the pylorus was an acute ulcer which was irregular and 5 cm. in diameter. The ulcer showed round edges and its base was covered with pink granulation tissue. Sections of the stomach showed diffuse infiltration by reticulum cell sarcoma. There were numerous irregular nodules of white tumor tissue projecting from the mucosa of the jejunum and ileum. The remainder of the gastrointestinal tract showed nothing noteworthy. The pancreas weighed approximately 100 grams and the head was involved in the neoplastic process.

The left adrenal gland was almost completely replaced by neoplasm, with only a small amount of normal tissue remaining in the lower pole. The right adrenal appeared normal on gross examination. The left kidney weighed 165 grams and the right 145 grams. The capsules of both

stripped easily and the surfaces showed several slightly elevated white nodules 0.5 cm. in diameter extending into the parenchyma.

Anatomic Diagnosis: Reticulum cell sarcoma involving stomach, heart, liver, kidneys, pancreas, prostate, adrenals, ileum; mesenteric and mediastinal nodes.

CASE 2: The patient was a 30-year-old white man who was well until November, 1945, when he began to have epigastric discomfort following meals. The discomfort was not relieved by belching or by food. Shortly after its onset, his stools became tarry. The epigastric pain became progressively more severe, and he began to complain of easy fatigue and weakness. On Dec. 21, 1945, the patient was admitted to a private hospital for study.

Physical examination revealed a well-developed and well-nourished white man in no acute distress. Essential positive findings were confined to the abdomen which was slightly distended. The lower half was tympanitic and there was slight tenderness to the left of the epigastrium. No abnormal masses were palpable.

Examination of the blood showed a red cell count of 3,700,000 with 11.6 Gm. of hemoglobin. The white cell count was 13,000, with 76 per cent polymorphonuclear leucocytes, 20 per cent lymphocytes, and 4 per cent eosinophiles. Stool examination was positive for occult blood. Urinalysis was negative. Gastric analysis showed hemolyzed blood and free hydrochloric acid. Because of the evidence of gross bleeding, immediate radiographic examination of the stomach was made. The impression of the examiner was prepyloric gastric ulcer on the lesser curvature, and the patient was treated medically for bleeding gastric ulcer.

During this hospital admission, the patient failed to improve. Periodic stool examinations showed occult blood, and on the fifth hospital day, icterus of the sclera and skin was seen. On the tenth hospital day, palpation of the abdomen revealed a mass under the left costal margin and in the left epigastrium, which was tender and firm. Examination by barium enema showed this mass to be extrinsic to the large bowel. On the fifteenth hospital day the patient was discharged to his home where observation was continued. During the following week, the mass became larger, the icterus more pronounced, and the patient began to vomit. On one occasion, a small clot of blood was noted in the vomitus. Because he was growing worse, further hospitalization was advised and he was admitted to Oliver General Hospital on Jan. 10, 1946.

On this admission the patient was acutely ill. His temperature varied from 101° to 103° Fahrenheit. The pulse rate was 140 per minute and respirations 28 to 30 per minute. The impression on admission was ruptured peptic ulcer with liver abscess and possible peritonitis.

On Jan. 25, 1946, an exploratory laparotomy was performed. A small amount of free fluid was found in the peritoneal cavity. The liver was enlarged and appeared congested. The pancreas, gall bladder, and spleen were normal. The posterior wall of the stomach was markedly thickened, firm, and involved in a diffuse, infiltrating neoplastic process. The anterior wall of the stomach in the region of the cardia was also involved in this process. There was nothing to suggest any involvement outside of the stomach wall. The stomach was opened and a thickened nodular mass was felt on the posterior wall. A biopsy was made and because the neoplastic infiltration was so extensive, gastric resection was impossible.

A report of the microscopic examination of the tissue was as follows: "Section of portion of stomach shows almost complete replacement of the glandular structures, which in parts are intact, by rounded to irregularly polygonal neoplastic cells, the outlines of which are indistinct while the nuclei are quite prominent, generally hyperchromatic, and show numerous mitoses. There is no stomal reaction and the neoplastic cells are arranged in no particular pattern. There is a considerable amount of granular debris throughout the neoplastic fields." Diagnosis: Reticulum cell sarcoma of stomach.

On Feb. 1, 1946, the patient was transferred to Walter Reed General Hospital for roentgen therapy. On admission he was markedly icteric, emaciated, dehydrated, and acutely ill. There was moderate distention of the abdomen and an epigastric mass was palpable.

From Feb. 4, 1946, to Feb. 19, 1946, he received roentgen therapy amounting to 3,600 roentgens (measured in air with back scatter) through a 15 × 20 cm. anterior epigastric portal. The following physical factors were employed: 1,000; 3 M; 70 cm. target-skin distance; 3 mm.

tungsten filter; half-valve layer = 3.6 mm. lead; 88 roentgens per minute. A tissue dose of 2,412 roentgens was delivered into the stomach in a period of sixteen days.

He improved moderately, and the epigastric mass decreased about 75 per cent in size. The distention disappeared, his appetite increased, his icterus diminished, and he began to have daily bowel movements. Following roentgen therapy, an x-ray examination showed marked improvement in the appearance of the stomach. Hypertrophy of the gastric rugae was seen and numerous nodular defects were noted in the cardia. The patient's temperature remained normal following roentgen therapy, but there was persistent tachycardia of 120 to 140 beats per minute. Unfortunately, neither an electrocardiogram nor a chest roentgenogram was obtained. On the morning of March 15, 1946, the patient became lethargic, drowsy, and shortly afterward expired.

Post Mortem Examination: The abdominal cavity contained approximately 1,000 c.c. of clear straw-colored fluid. There was marked distention of the loops of the small bowel. Numerous nodes measuring from 1 to 3 cm. in size were seen, and several small nodes were present in the periaortic chain.

The heart weighed 265 grams. In several areas just under the epicardium there were firm, pinkish-white tumor nodules, 1 to 2 cm. in diameter, the largest being located in the right ventricle. On section, the myocardium was pale red and infiltrated with numerous areas of pale neoplastic tissue (Figs. 5A and 5B).

The fundus of the stomach was thickened, firm, and pale. Throughout the entire stomach there were occasional acute ulcers, approximately 1 cm. in diameter. Numerous tumor nodules were noted on the mucosal surface. The pancreas was intimately adherent to the tumor mass in the wall of the stomach and on section showed marked neoplastic involvement.

Both kidneys were enlarged and densely infiltrated by tumor tissue, so that only occasional areas of normal renal parenchyma were seen. The adrenal glands were also the seat of diffuse metastatic disease.

Final Diagnosis: Reticulum cell sarcoma involving the stomach, heart, liver, pancreas, kidneys, adrenals, and mesenteric, mediastinal, and periaortic lymph nodes.

DISCUSSION

The ante-mortem diagnosis of metastatic cardiac neoplasm is unusual. In Case 1 of this report, in which the clinical diagnosis of metastatic tumor of the heart was made by one of us (I. B. B.), suspicion was aroused because of the sudden onset of dyspnea and the occurrence of a third sound which was interpreted as a gallop rhythm. Certain workers have reported a third sound in heart block, probably auricular in origin, the exact physiologic mechanism of which is not clear. Nevertheless, the clinical findings warranted further investigation, so that an electrocardiogram was obtained which showed a complete A-V heart block. In addition, the patient rapidly developed cardiac enlargement. This finding in conjunction with the electrocardiographic changes in a patient with known reticulum cell sarcoma was enough to warrant a definite diagnosis of cardiac metastasis. Yater¹ has suggested that in every case of heart block, particularly when the block is complete, the possibility of tumor should be seriously considered.

We strongly support the view of Scott and Garvin¹⁸ that any patient with malignant disease who develops cardiac failure should be suspected of having cardiac metastasis. Repeated physical examination of the heart, roentgen examination, and, particularly, serial electrocardiographic observation in cases of this type would probably result in a much greater number of correct ante-mortem diagnoses.

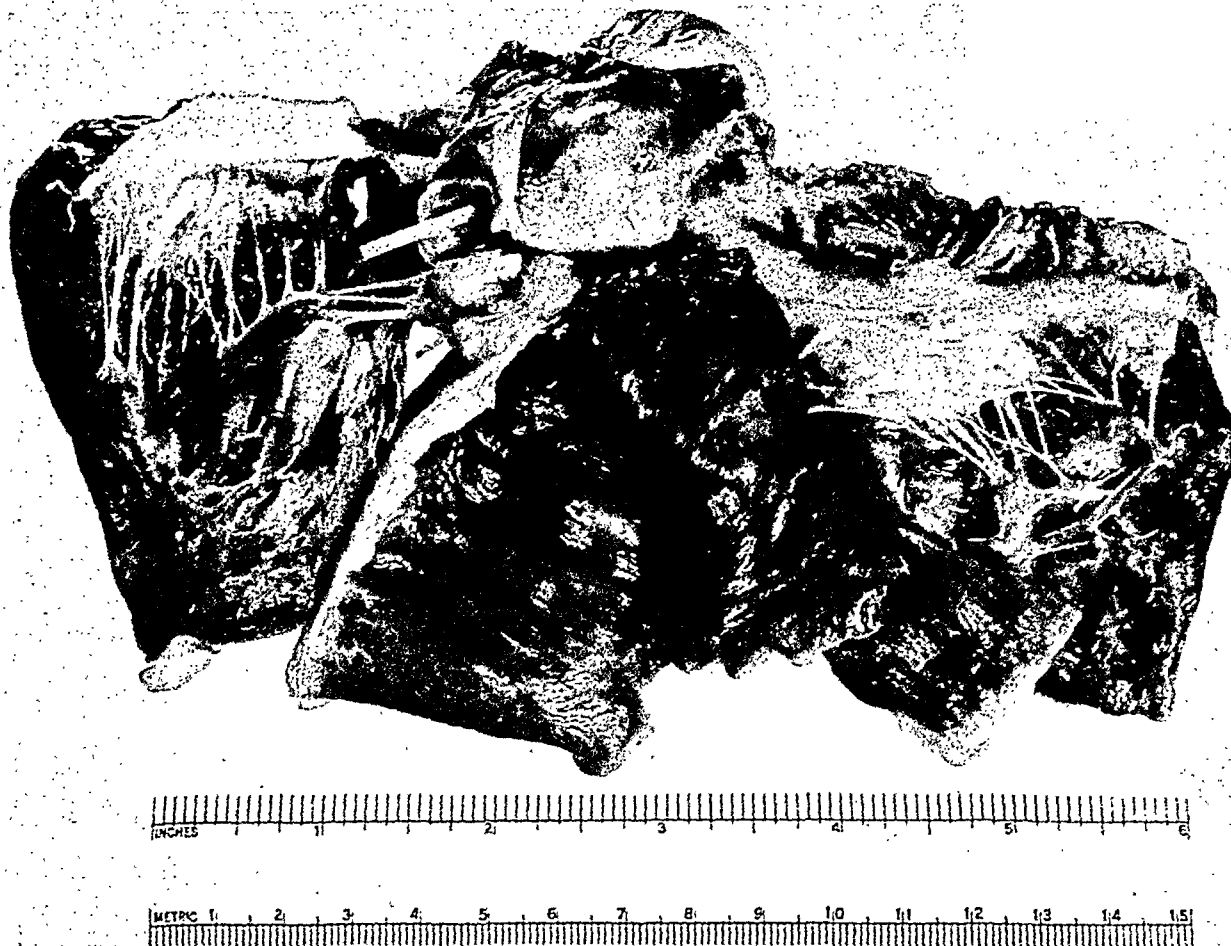


Fig. 5A.—Case 2. Gross specimen of heart following section showing pale nodular areas in the inter-ventricular septum. A large metastatic nodule in the right atrium is indicated by the marker.

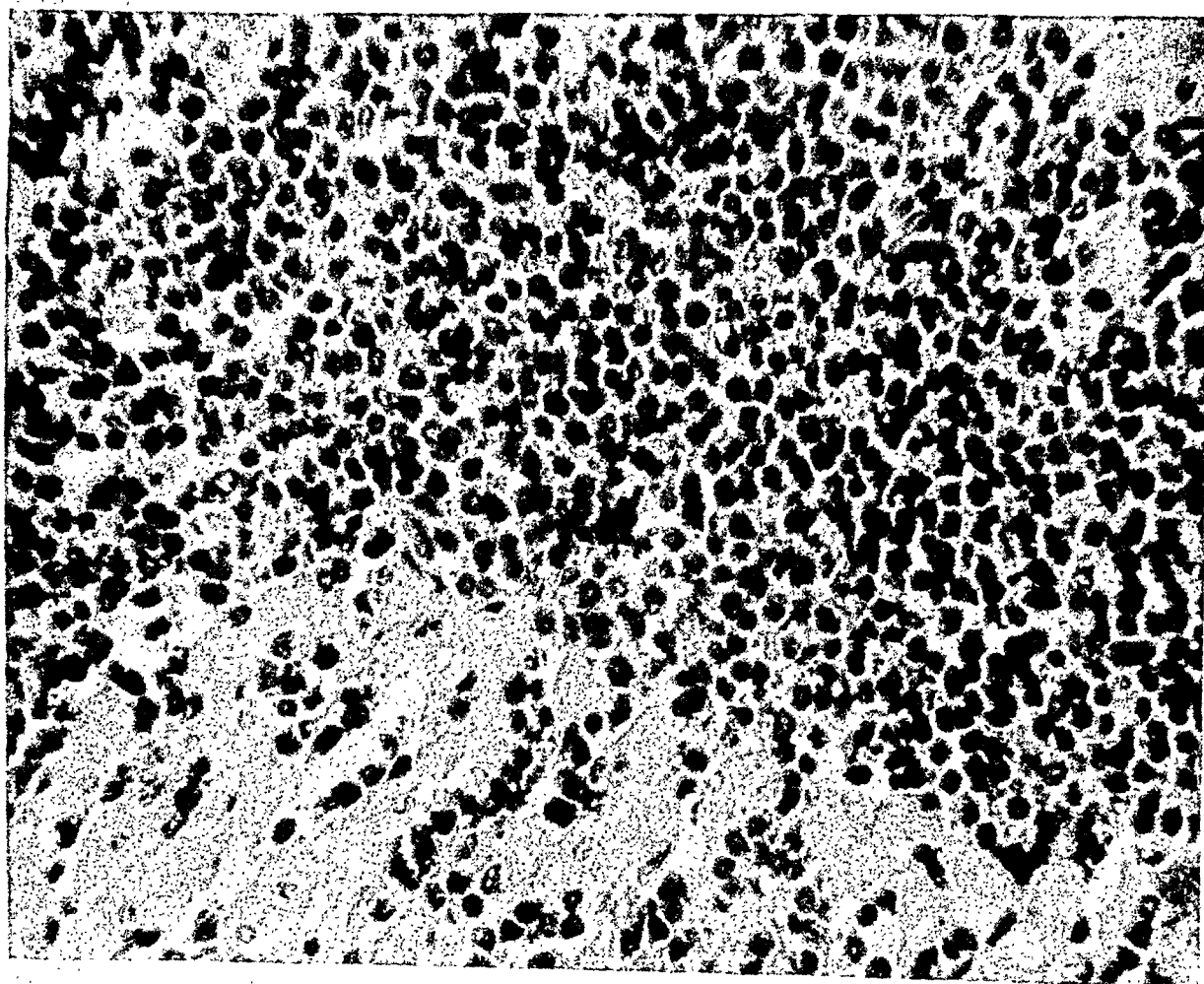


Fig. 5B.—Case 2. High power (x440) photomicrograph of myocardium showing infiltration by reticulum cell sarcoma.

Although reports in the literature concerning metastasis to the heart in reticulum cell sarcoma are scanty, we are of the opinion that it occurs much more frequently than is reported. Certainly autopsy experience demonstrates that reticulum cell sarcoma often involves kidneys, adrenals, liver, and more rarely, the heart. Whether these widespread lesions should be regarded as metastatic is an unsettled matter. Many believe that this secondary involvement may take place wherever aggregates of reticuloendothelial tissue are present in the body, and that this involvement is excited by the same factor that is responsible for the primary tumor. Should one accept the view that the secondary lesions are metastatic, the possibility of hematogenous dissemination of this disease is suggested.

Both of our cases showed marked similarity in the distribution of their disease. The presence of large subcutaneous neoplastic nodules in Case 1 was an interesting and unusual finding. This type of lesion occurs rarely in many anaplastic and highly malignant carcinomas and sarcomas, other than reticulum cell sarcoma, in the terminal phases of disease.

Recently, Cash and Rappoport²² reported a case of reticulum cell sarcoma of the stomach and commented upon its rarity. Both cases reported here showed widespread gastric involvement. It is interesting to note, however, that the second case is probably primary reticulum cell sarcoma of the stomach. It meets the criteria for the latter diagnosis, in our opinion, and the paucity of disease found at autopsy in the retroperitoneal nodes, from which the stomach is most frequently involved by reticulum cell sarcoma, supports this view. Additional support is gained from the findings at laparotomy, at which time the entire pathologic process was confined to the stomach.

The variation in the radiographic appearance of the gastric disease is in accordance with the experience of others. Reticulum cell sarcoma involving the stomach may present itself as a diffuse infiltrating process involving the entire stomach. In this type of disease there is marked thickening of the mucosal folds and hypertrophy of the gastric rugae. Clinically, the impression is usually peptic ulcer and the roentgenograms in this type of disease are usually interpreted as diffuse hypertrophic gastritis. Another type less frequently seen in reticulum cell sarcoma is that of multiple submucosal nodular papillary infiltration. Radiographically, numerous polypoid lesions may be demonstrated with careful spot film techniques. Case 1 represents the lesion most frequently encountered in reticulum cell sarcoma of the stomach. Radiographically, one finds a huge cauliflower malignant lesion which cannot be differentiated from gastric carcinoma.

SUMMARY

Two cases of reticulum cell sarcoma involving the heart and stomach are reported. Both cases were explored surgically and inoperable disease was found. They were treated with palliative supervoltage roentgen therapy with only temporary improvement. At autopsy, widespread disease was found, with metastasis to the heart. The cardiac involvement was diagnosed during life, in one case, on the basis of physical, electrocardiographic, and radiographic evidence.

REFERENCES

1. Yater, W. M.: Tumors of the Heart and Pericardium, *Arch. Int. Med.* 48:627, 1931.
2. Lisa, J. R., Hirschhorn, L., and Hart, C. A.: Tumors of the Heart, *Arch. Int. Med.* 67:91, 1941.
3. Doane, J. C., and Pressman, R.: Ante-Mortem Diagnosis of Tumors of the Heart, *Am. J. M. Sc.* 203:520, 1942.
4. Ravid, J. M., and Sachs, J.: Tumors of the Heart, *AM. HEART J.* 26:385, 1943.
5. Zemansky, A. O., Jr.: Examinations of Fluids for Tumor Cells, *Am. J. M. Sc.* 175:489, 1928.
6. Hsiung, J. C., Szutu, C. Z., Hsieh, C. K., and Lieu, V. T.: Metastatic Tumors of the Heart, *Chinese M. J.* 57:1, 1940.
7. Shelburne, S. A., and Aronson, H. S.: Tumors of Heart, *Ann. Int. Med.* 14:728, 1940.
8. Reuling, J. R., and Razinsky, L.: Metastatic Bronchiogenic Carcinoma of Heart, *AM. HEART J.* 21:470, 1941.
9. Greiner, D. J.: Reticulum Cell Sarcoma Involving Heart and Pericardium, *Bull. School Med. Univ. Maryland* 25:44, 1940.
10. Cabot Case Records, Case Number 27281, *New England J. Med.* 225:76, 1941.
11. Rosenbaum, F. F., Johnston, F. D., and Alzamora, V. V.: Persistent Displacement of the RS-T Segment in a Case of Metastatic Tumor of the Heart, *AM. HEART J.* 27:667, 1944.
12. Hamilton-Paterson, J. L., and Castleden, L. I. M.: Intracardiac Tumors, *Brit. Heart J.* 4:103, 1942.
13. Lymburner, R. M.: Tumors of the Heart: Histopathological and Clinical Study, *Canad. M. A. J.* 30:368, 1934.
14. Pollia, J. A., and Gogol, L. J.: Some Notes on Malignancies of the Heart, *Am. J. Cancer* 27:329, 1936.
15. Helwig, F. C.: Tumors of the Heart, *J. Kansas M. Soc.* 36:265, 1935.
16. Burke, E. M.: Metastatic Tumors of the Heart, *Am. J. Cancer* 20:33, 1934.
17. Willis, R. A.: The Spread of Tumors in the Human Body, London, 1934, J. & A. Churchill, Ltd.
18. Scott, R. W., and Garvin, C. F.: Tumors of the Heart and Pericardium, *AM. HEART J.* 17:431, 1939.
19. Ritchie, G.: Metastatic Tumors of the Myocardium, *Am. J. Path.* 17:483, 1941.
20. Herbut, P. A., and Maisel, A. L.: Secondary Tumors of the Heart, *Arch. Path.* 34:358, 1942.
21. Fishberg, A. M.: Auricular Fibrillation and Flutter in Metastatic Growths of Right Auricle, *Am. J. M. Sc.* 180:629, 1930.
22. Cash, I. I., and Rappoport, H. E.: Reticulum Cell Sarcoma of the Stomach, *Gastroenterology* 6:40, 1946.

Abstracts and Reviews

Selected Abstracts

Pendergrass, E. P., Griffith, J. Q., Jr., Padis, N., and Barden, R. P.: The Indications for Irradiation of the Pituitary Gland in Patients With Arterial Hypertension. Am. J. M. Sc. 213:192 (Feb.), 1947.

Pituitary irradiation as a treatment for high blood pressure was given to 142 patients without untoward effect, although three patients with papilledema showed severe, acute but transient reactions indicating increased intracranial pressure. Only ninety-three patients were adequately followed for a period varying from three to fifty-six months. About half of these persons showed improvement in blood pressure and clinical condition. All of these individuals were selected on the basis of a positive test for antidiuretic hormone in the serum.

From a consideration of other studies and of the results of varying roentgen dosage, it is concluded that the chance of benefit from radiation therapy to the pituitary in hypertension should be at least 75 per cent if cases are selected according to the following criteria: (1) Positive bioassay for antidiuretic hormone in the serum; (2) a roentgen dosage of 1000 R delivered into the hypophysis (2000 R in air), to be repeated in three months if the test for antidiuretic hormone in serum has not become negative in that time; (3) a negative bioassay for gonadotropic hormone in serum, at the level of 330 million units per 100 c.c. of serum; (4) a normal renal function as shown by a plasma creatinine, by the method of Steinitz and Turkand, of 1 mg. per cent or less, (presumably a test of urea clearance would be equally satisfactory); and (5) good clearance of injected dye from each kidney as shown by urography. Three illustrative case reports are presented.

DURANT.

Wirtschafter, Z. T., and Widmann, R.: The Elaboration of Histamine In Vivo in the Treatment of Peripheral Vascular Disorders—A Preliminary Report. J.A.M.A. 133:604 (March), 1947.

These authors repeated the work of R. H. Katz, who suggested the use of intravenous diethyl ether for the treatment of impending ischemic gangrene and other peripheral vascular disorders. Serum obtained from patients during treatment produced wheals and flares on intradermal injection into normal, nonallergic subjects and caused contraction of the isolated guinea pig intestine. These findings suggested a histamine release during the period of diethyl ether administration. Twelve consecutive unselected cases of definite peripheral vascular disease were treated by this method. There was improvement in five. In seven patients the pain was not relieved throughout the twenty-four hour period, and in eight, unfavorable reactions were noted.

In 1937, Holtz reported the conversion of histidine to histamine, in vitro, by the action of ascorbic acid. To obviate all the complications of intravenous ether, the authors attempted to produce this reaction in vivo. Patients were first given 500 mg. of sodium ascorbate intravenously. This was followed by the intramuscular injection of 5 c.c. of a 4 per cent aqueous solution of 1(-) histidine monohydrochloride simultaneously with the subcutaneous injection of 100 mg. of sodium ascorbate. The subsequent regimen consisted of giving the two organic compounds in the manner described every four, six, eight or twelve hours, depending on the severity of the clinical findings. In addition, patients daily received 600 mg. of ascorbic acid orally.

To demonstrate the presence of histamine, the serum and urine of the subjects on the regimen were injected intradermally into normal nonallergic individuals, and in all cases typical and decidedly strong wheals and flares were produced.

Eleven consecutive cases of definite peripheral vascular disease studied by the authors comprise the subject of this preliminary report. These authors report that all of these patients have responded favorably, up to date, to the therapy described and have not required amputations, and the relief of intractable pain has occurred within six hours to three days after the institution of treatment. These authors also state that patients with gangrene have shown a response most quickly, describing a sensation of increased warmth in the affected limbs which has been readily observed on examination.

These authors believe that the parenteral administration of histidine monohydrochloride and sodium ascorbate is worthy of investigation, not only in peripheral vascular disease as such, but whenever the capillary loop is impaired, and also when a collateral circulation is imperative for the repair of or reversal of the pathologic process. With this in view, application of this regimen is now under investigation in coronary artery disease, angina pectoris, hypertension, glomerular nephritis, mesenteric thromboses, cerebral vascular accidents, Parkinson's disease, multiple sclerosis, thrombosis of the central retinal vein, Ménière's disease, migraine, and eclampsia.

BELLET.

Fastier, F. N., and Smirk, F. H.: Circulatory Properties of Iso-Thioureas, Guanidines, Iso-Ureas and Amidines. *J. Pharmacol. & Exper. Therap.* 89:256 (March), 1947.

S-methyl iso-thiourea has been found to cause a sustained rise in blood pressure when given intravenously. The mechanism of its action and the action of ten other closely related chemical compounds on the circulatory system form the basis of this report.

The compounds may be divided into four groups: (1) S-methyl iso-thiourea; (2) methyl-guanidine; (3) o-methyl iso-urea; and (4) acetamidine. The eleven compounds were tested upon intact dogs, cats, isolated rabbit intestine, and pithed hind quarters of rats perfused with oxygenated Ringer-Locke solution through the abdominal aorta.

All preparations were found to have pressor activity in the intact animal, since they caused contraction of atropinized rabbit gut and produced a rise in pressure of perfusion fluid in the hind quarter preparation of the pithed rat. This would correspond to a rise in blood pressure in the intact animal, excluding central nervous control. Ergotoxin did not inhibit this rise. Most of the compounds enhanced the action of adrenalin pressor response in the intact animal; they either increased or diminished the response of perfused blood vessels to injections of adrenalin.

The evidence suggests the action of this group of closely related compounds is probably peripheral. Their close chemical relationship and similar circulatory action suggests that they may possess potentially useful properties as a pharmacologic group.

GODFREY.

Anrep, G. V., Barsoum, G. S., Kenawy, M. R., and Misrahy, G.: Therapeutic Uses of Khellin. *Lancet* 1:557 (April 26), 1947.

Chemical analyses have shown the active principle of khellin to be a di-methoxy-methyl-furano-chromone and that the preparation thus belongs to the same group as coumarines and possibly flavones. Khellin causes a conspicuous and long relaxation of visceral smooth muscle, including the intestines, uterus, bile ducts, bronchi, and, especially, ureters.

In 1945, a fresh interest in khellin arose as the result of the discovery that it acts as an extremely potent coronary vasodilator which, in doses used, has no effect on the general blood pressure and does not increase the oxygen requirements of the heart (Anrep and Misrahy, 1945). This action of khellin lasts many hours.

A complete and prolonged relief was obtained in forty-one out of forty-five cases after a single intramuscular injection of 200 to 300 milligrams. Complete relief is given five to fifteen minutes after the injection and usually lasts about twenty-four hours. Repeated daily administrations of khellin by injection or by mouth conspicuously reduce the number and severity of the

attacks. In obstinate cases of severe status asthmaticus a second and sometimes a third dose has to be given at intervals of one or two hours to produce relief.

Since the publication of the observations of the authors a considerable number of preparations of *Ammi visnaga* are being offered to the public without proper control or standardization. The authors issue a warning that crude extracts of *Ammi visnaga* may cause undesirable effects, especially when used for intramuscular injections in concentrated solutions. In animals such extracts may cause long-continued oliguria. Taken by mouth, crude extracts and decoctions often cause severe gastric irritation and nausea, and sometimes diarrhea. Therefore, all preparations of *Ammi visnaga* to be used by mouth or by injection should be freed from injurious impurities, and the final concentration of the active principle (khellin) should be standardized. Extracts for oral or intramuscular administration should contain not less than 50 mg. per cubic centimeter.

BELLET.

Mills, P. J. W.: Hypertensive Headache Treated With Potassium Thiocyanate. Lancet 1:324 (March 15), 1947.

The author reports that potassium thiocyanate is known to be a normal physiologic constituent of the blood and saliva and, therefore, acts by replacing the salivary thiocyanate, which is low in many cases of malignant hypertension. Thiocyanate is also a vasodilator, but the symptomatic relief it gives does not correspond to the slight lowering of blood pressure that may occur.

The symptoms which respond most readily to this drug are headache and dizziness. The effect on the blood pressure varies widely. The drug usually causes some lowering of both systolic and diastolic readings after one or two weeks' treatment, but this lowering of the pressure is not maintained, although symptoms continue to be relieved. There is no definite relationship between lowering of the pressure and the relief of symptoms.

After a study of twenty-seven cases of benign hypertension and ten cases of malignant hypertension, in which headache and giddiness were prominent symptoms, the author reaches the conclusion that this drug has a definite but limited place in the treatment of hypertension and should be restricted to cases in which hypertensive headache is a predominant and troublesome symptom and does not respond to simpler forms of therapy.

He states that this drug does not affect the course of the disease; nor does it permanently lower the blood pressure even in cases in which there is much symptomatic improvement.

BELLET.

Zondek, H.: Mixed Thyroidism. Acta med. orient. 5:387 (Dec.), 1946.

The author terms a condition involving a mixture of hyper- and hypothyroidism mixed thyroidism. This condition was originally described by this author in 1924. Zondek reports cases presenting evidence of both hyper- and hypothyroid traits in different variations and combinations, bringing attention to the fact that tachycardia, tremor, nervous hyperexcitability, and both high and low basal metabolic rates may be coupled with obesity and hypercholesterolemia.

The author theorizes as to the explanation of this condition and suggests the following theories: (a) disturbance in the normal balance of the pituitary and thyroid, or (b) production of a thyroid hormone which differs from the normally produced hormone from both biologic and chemical viewpoints.

The treatment of cases of "mixed thyroidism" varies according to which disturbance predominates in the clinical picture. Generally, the basal metabolic rate should be considered as the main guide to therapy.

Cases are reported in which both hyper- and hypothyreotic signs are concurrently found in varying combinations, for example, obesity, hypercholesterolemia, and low basal metabolic rates with tachycardia and exophthalmos.

BELLET.

Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: *Physiological Studies in Congenital Heart Disease II. Results of Preoperative Studies in Patients With Tetralogy of Fallot.* Bull. Johns Hopkins Hosp. 80:121 (Feb.), 1947.

This report deals with the results of preoperative studies on patients with congenital heart disease in whom clinical and physiologic examinations indicated the presence of reduced pulmonary blood flow.

The volume of blood flowing through the pulmonary arteries was calculated according to a previous formula (Bull. Johns Hopkins Hosp. 80:107, 1947.) in a total series of 120 patients with pulmonic stenosis. In thirty-six of forty-eight consecutive studies selected for presentation in this paper, the flow through the pulmonary artery per square meter of body surface, according to the formula, showed marked variations above and below the values for the normal cardiac index.

A comparison of the data obtained for systemic flows with those for the pulmonary artery demonstrated that the former exceeded pulmonary artery flow by from 0 to 9.7 liters per minute. This indicated that in the tetralogy of Fallot some of the returning mixed venous blood, unable to pass through the stenosed pulmonary artery into the lung, coursed through the interventricular septal defect and the overriding aorta directly into the systemic circulation.

Values for pulmonary capillary flow were also calculated according to the formula and, in most of the younger individuals, agreed closely with those determined for pulmonary artery flow. In the majority of older patients, however, pulmonary capillary flow exceeded pulmonary artery flow, indicating that the lungs received blood from sources other than the pulmonary artery. It seemed probable that the collateral circulation to the lung represented an important factor in the physiologic adjustments of these individuals to their abnormally low pulmonary artery flow.

Intracardiac and systemic blood pressures were obtained in a series of twenty-two patients with clinical and physiologic evidence of tetralogy of Fallot. It was shown that the right intraventricular systolic pressure was elevated in every instance except one; pressures recorded ranged from 20 to 110 mm. above the normal values of 18 to 28 mm. of mercury.

The oxygen consumption in the great majority of individuals with decreased effective pulmonary flow was reduced. The basal metabolic rate calculated from these figures ranged as low as -48 per cent. This finding was of considerable interest since it suggested that the decrease in the overall metabolic processes might be the result of prolonged anoxemia. The basal metabolic rate of individuals with reduced effective pulmonary blood flow increased considerably following performance of the Blalock-Taussig operation.

A standard exercise test was performed in a series of twenty-one patients. The ratio of oxygen consumed per liter of ventilation during exercise fell below its resting value and the carbon dioxide produced per liter of ventilation also declined in sixteen individuals. This was contrary to observations on normal individuals in whom the standard exercise resulted in a significant increase in the oxygen consumption and a slight rise in the carbon dioxide production. This demonstrated that the fall in arterial oxygen saturation after exercise observed in patients with normal rate of flow through the lung must have been caused by increased shunting of venous blood into the systemic circulation.

The results of the tests described demonstrate a reduction in pulmonary artery flow of from 1,000 to 2,000 c.c. below the normal cardiac index, depending on the degree of the stenosis. In normal individuals, variations in the overall circulating volume of blood flow are usually the result of functional changes. With varying degrees of pulmonic stenosis and interventricular septal defect, however, the systemic blood flow depends to a large extent on the volume of the intracardiac shunt. In most cases of tetralogy of Fallot, the systemic flow exceeds that through the pulmonary artery, indicating that the overall direction of the intracardiac shunt is from right to left. Consequently, the systemic blood flow will be particularly high in individuals with severe pulmonic stenosis, large interventricular septal defects, and marked overriding of the aorta.

Intraventricular pressure curves obtained in pulmonary stenosis revealed the systolic pressure in the right ventricle to be 20 to 110 mm. Hg above normal values. It was observed that in eight out of a total of twenty-two recordings the general level of the ventricular diastolic pressure was elevated above the minimum values occurring early in diastole. The results illustrated that

the peripheral resistance varied while the mean systemic pressure showed only small variations from the normal. As the systemic flow increased, the peripheral resistance declined logarithmically.

The interrelationship of venous-arterial shunts and decreased pulmonary blood flow in the production of anoxemia is stressed. The basic action of both factors was shown to be through their effect on volume of mixed venous flow through the lung (the effective pulmonary blood flow) representing the volume of systemic blood, which after passing through the right auricle, reaches the alveolar capillaries. A decrease in pulmonary capillary flow existing in conjunction with intracardiac shunts contributes to arterial oxygen saturation only by reducing the effective pulmonary blood flow. A large right-to-left shunt will cause anoxemia for the same reason.

BELLET.

Cournand, A., Himmelstein, A., Riley, R. L., and Lester, C. W.: A Follow-Up Study of the Cardiopulmonary Function in Four Young Individuals After Pneumonectomy. J. Thoracic Surg. 16:30 (Feb.), 1947.

Several years ago three reports were published which provided a physiologic background for some of the clinical problems posed by the ablation of one lung. The third report dealt with the changes in lung volume, and in ventilatory and alveolorespiratory functions at rest and during moderate and exhausting exercise in three young individuals who were still in their period of growth when studied a few years after pneumonectomy. A follow-up study is presented here and a fourth case has been added. These individuals have now reached late adolescence or adult age. In these four cases, the left lung was resected during childhood, in one or in several stages, for bronchiectasis or pulmonary suppuration.

The method used consisted in the study at regular intervals of the lung volumes, the ventilatory efficiency of the chest bellows, the efficiency of alveolar ventilation, and the state of respiratory gas exchanges in the lung and in the arterial blood, at rest and during a moderate and an exhausting type of exercise. At the time of the most recent study the right ventricular pressures and the pulmonary blood flow were measured in three of the four subjects under basal conditions.

In two patients who developed a moderate degree of pulmonary distention, the only significant findings were a reduction in breathing reserve from normal and a marked degree of oxygen unsaturation in the arterial blood, brought out by a very strenuous type of exercise. The moderate degree of pulmonary distention, which increased slightly in one subject during the period of growth of his lung, has not progressed during the last three years. Performance of one subject who did not show any evidence of pulmonary distention was indistinguishable from that of a normal individual under the same strenuous circumstances. No significant degree of hypertension in the lesser circulation has developed in the six to ten years that have elapsed since operation.

In individuals with only one lung, preservation of normal pressure-flow relationship may be achieved in two ways which may complement each other: (a) by an increase in the number of capillaries, or (b) by an increase in their size. By a simple calculation, based on Poiseuille's law, it can be shown that an increase of only 16 per cent in the diameter of the capillaries of one lung would allow a 100 per cent increase in pulmonary blood flow to occur without any change in pressure in the pulmonary artery.

BELLET.

Hoyne, A. L., and Grown, R. H.: Penicillin for Scarlet Fever. J.A.M.A. 133:661 (March), 1947.

These authors studied 548 patients with scarlet fever. Of that number, beside the 116 who were given penicillin, sixty-nine were treated with convalescent scarlet fever serum, forty-eight with one of the sulfonamide drugs, and two with scarlet fever antitoxin; the remaining 312 who were given neither serum nor drugs served as controls. All patients were treated in the same hospital, in a given period of time; in each group there were mild, moderate, and severe instances of the disease, and evaluations in respect to treatment were based on the impressions formed by the same observers through personal contact and study. Among the entire group, only 4.2 per

cent suffered from suppurative otitis media during the entire course of their illness. The disease was mild in most instances, and only one death occurred in the series of 548 patients.

The average number of days of illness was higher for the penicillin-treated group; however, the average number of days of the rash was less in this group. Penicillin exerted no special influence on temperature. Fewer complications followed its use than occurred with other forms of therapy, though the penicillin group had the highest percentage of complications at the time of hospitalization.

Sulfonamide-treated patients were not protected against further infection; the percentage of complications which developed after the institution of treatment in the group given penicillin was less than half as great as that for those patients who received either sulfonamide compounds or convalescent serum.

The authors state that penicillin therapy is equally as good a therapeutic agent for scarlet fever as is convalescent serum, and is superior to the sulfonamide group of drugs.

BELLET.

Epstein, B. S.: Rheumatic Mitral Valve Disease Without Cardiac Enlargement. Radiology 48:249, 1947.

The diagnostic problem of mitral valve disease is sometimes very perplexing and the aid of the roentgenologist is often sought. It should be recognized by both the internist and roentgenologist that in mitral valve disease there may be no visible alteration in the radiographic appearance of the heart, just as mitral murmurs may be absent or atypical.

The author reviews twenty-five cases of well-defined mitral stenosis in which the roentgenographic appearance was normal. Fluoroscopy and teleroentgenograms, including the measurement techniques of Newcomer and Newcomer and of Ungerleider and Gruber, were used. The author quotes various autopsy reports of well-defined mitral and aortic valvular disease with no cardiac enlargement. He also points out the fact that although left atrial dilatation is the earliest roentgen sign of mitral valvular disease, there is a small group of patients with mitral stenosis who have cardiac enlargement without left atrial dilatation.

The conclusions are that if the murmurs are characteristic the diagnosis of mitral valve disease must be made even in the absence of any roentgen signs. Conversely, if cardiac enlargement is observed roentgenographically, the conclusion that organic heart disease is present must be reached even though the murmur may be atypical or minimal.

ZION.

Heymans, C., Pannier, R., and Verbeke, R.: The Influence of the Anticholinesterases, Prostigmine, Eserine and Di-isopropylfluorophosphate, and of Atropine on the Central and Peripheral Transmission of Nervous Excitation. Arch. internat. de pharmacodyn. et de therap. 72:405 (Sept.), 1946.

The authors studied the influence of three anticholinesterases, prostigmine, eserine and di-isopropylfluorophosphate, and of atropine on the transmission of nervous excitation at the level of the centers and peripheral elements of different parts of the nervous system which have been considered as cholinergic in their mechanism of action or transmission. The experiments were performed on anesthetized dogs and on the isolated perfused head and isolated perfused carotid sinus.

It was found that prostigmine does not enhance the direct or reflex excitation of the cardio-inhibitory of respiratory centers, nor does it affect the transmission of vasomotor reflexes induced by the carotid sinus pressoreceptors. Atropine does not affect the direct or reflex excitation of the cardioinhibitory or respiratory centers. The very active anticholinesterase, di-isopropylfluorophosphate, in doses which inhibit completely the cholinesterases of blood and tissue, sensitizes to anticholine but does not increase the peripheral excitability of the vagal cardioinhibitory nerve. It does not affect the cardiovascular and respiratory reflexes induced by the carotid sinus pressoreceptors, nor does it produce hypersalivation, myosis, hyperperistalsis, or bronchospasm.

Injection of prostigmine or eserine after inhibition of cholinesterases by preliminary administration of di-isopropylfluorophosphate still produces bradycardia and other vagal effects. These

reactions are neutralized by atropine and cannot be related to the anticholinesterase activity of prostigmine and eserine. Di-isopropylfluorophosphate appears to sensitize the dog to the pharmacologic action of prostigmine and eserine.

These results are contrary to the theory that a cholinergic mechanism is concerned in the transmission of the nervous stimulations which have been tested.

LAPLACE.

Heymans, C., Pannier, R., and Vanostende, A.: The Influence of Pulmonary Hyperventilation on the Vasomotor Reflexes of the Carotid Sinus and on the Tonus of the Vasomotor Center. Arch. internat. de pharmacodyn. et de therap. 72:430 (Sept.), 1946.

The effect of hyperventilation on the vasomotor reflexes of the carotid sinus and on the tonus of the vasomotor centers was studied in a series of experiments on anesthetized dogs. It was found that when mechanical interference with the pulmonary and thoracic circulation is avoided, hyperventilation, alkalosis, and acapnia do not produce any fall of the general arterial blood pressure. The central vasoconstrictor tone and the vasomotor reflexes initiated by the carotid sinus pressoreceptors are only slightly, if at all, depressed by hyperventilation, alkaloses, and acapnia. The influence of anesthetics on the role of the vasomotor reactions in the adaptation of the circulation during hyperventilation, acapnia, and alkalosis is discussed.

LAPLACE.

Heymans, C., and Delaunois, A. L.: The Influence of Arterial Work and Pressure on the Activity of the Cardiovascular and Respiratory Centers. Arch. internat. de pharmacodyn. et de therap. 72:444 (Sept.), 1946.

Experiments on intact anesthetized dogs and on the isolated perfused cephalic circulation indicated that changes in blood flow and blood pressure within physiologic but not extreme physiopathologic limits do not directly affect the activity of the respiratory or cardiovascular centers. The activity of these centers may be reflexly affected by variations in carotid arterial pressure through the mechanism of the carotid sinus. As previously demonstrated, the activity of the respiratory and cardiovascular centers may be affected by extreme modifications of cerebral blood flow, but this has no practical importance for the physiologic control of respiration and circulation.

LAPLACE.

Segers, M.: The Normal and Pathological Aspects of Conduction During the Refractory Phase. Arch. d. mal. du coeur. 39:260 (July-Aug.), 1946.

The duration of the refractory phase of conduction tissue was studied in a series of sixty-three electrocardiograms, which included auricular extrasystoles, sinus arrhythmia, and interpolated ventricular extrasystoles. Measurements were made of the P-Q and QRS intervals when two or more beats occurred in rapid succession.

It was found that in normal hearts the QRS interval was not prolonged during a succession of rapid beats. The refractory phase of intraventricular conduction tissue, therefore, is relatively short.

Block of the P wave was considered indicative of the duration of the absolute refractory phase of the bundle of His. In normal hearts, this phase was found to end at latest 0.20 second after the R wave of an auriculoventricular beat, and 0.25 second after the R wave of an idioventricular beat. Block of a P wave for longer than this interval was regarded as pathologic.

Lengthening of the P-Q interval was considered indicative of the duration of the relative refractory phase of the bundle of His. In normal hearts, this phase was found to end at latest 0.20 second after the end of the absolute refractory phase. Lengthening of the P-Q interval beyond this limit was considered pathologic.

The authors regard these observations as establishing the normal and pathologic limits of the refractory phase of conduction tissue in man.

LAPLACE.

Pect, Max M.: Results of Bilateral Supradiaphragmatic Splanchnicectomy for Arterial Hypertension. *New England J. Med.* 236:270 (Feb. 20), 1947.

The author considers neurogenic renal ischemia to be the fundamental mechanism of hypertension in the majority of cases. The abnormal stimulus originates in the hyperreactive autonomic centers of the brain and is transmitted to the kidneys by the splanchnic nerves. Raynaud's disease is analogous. Release of the neurogenic clamps is accomplished by bilateral supradiaphragmatic splanchnicectomy. This brief, one-stage operation has now been performed by the author in over 1,500 patients. The period of hospitalization and convalescence is short.

The best results most frequently have been attained in individuals under 30 years of age. Operation is rarely recommended in patients over 53 years of age unless symptoms are unusually distressing. In the clinical evaluation, the condition of the heart, kidneys, cerebral blood vessels, and eyes are evaluated with great care. Cardiac decompensation is a definite contraindication to surgery, unless it improves under therapy. Recent myocardial infarction is also a contraindication. Gross cardiac enlargement increases the operative risk, but results in these patients may be excellent. Patients with markedly contracted or polycystic kidneys or unilateral nonfunctioning kidney are rejected. A nonprotein nitrogen of over 45 mg. per cent is considered a definite contraindication to surgery, and those with levels above 40 are selected with hesitation. The operation is not performed on patients with chronic glomerulonephritis, but some of the most brilliant results have been obtained in patients in whom the hypertension was a sequel of "hypertensive toxemia of pregnancy." Patients with cerebral complications of short duration and without pronounced residual damage are considered suitable candidates, especially if under 50 years of age. Malignant hypertension, in the absence of far advanced cardiac or renal damage, is considered a definite indication for surgery.

The majority of the patients of the author's series have been followed for from one to twelve years. The results are given. Symptomatic relief has been striking. Significant improvement in reduction of blood pressure, improvement in ocular, renal, and cardiac status, relief of incapacitation, and probable prolongation of life are reported.

KAY.

Nickerson, J. L., Warren, J. V., and Brannon, E. S.: The Cardiac Output in Man: Studies With the Low Frequency, Critically Damped Ballistocardiograph, and the Method of Right Atrial Catheterization. *J. Clin. Investigation* 26:1 (Jan.), 1947.

A ballistocardiograph, mounted on a fluoroscopic table to facilitate right atrial catheterization, was constructed so that its undamped natural frequency was low and permitted, in addition, adjustment to a frequency of 1.5 cycles per second. In such a ballistocardiographic system only a minimum of overshooting occurs when the bed springs back from a displaced position to its resting position.

Of fifty-four observations made on thirty-two subjects without clinical evidence of heart disease, 87 per cent of the ballistic cardiac outputs fell within a range of ± 25 per cent of the values obtained by the catheter method (Fick principle). Of twenty-seven observations made in twenty-six patients with heart disease or myxedema, 60 per cent of the ballistic values fell within the 25 per cent range of the catheter values if the patients with aortic insufficiency were excluded from the calculations. In these latter patients, the ballistic outputs exceeded the catheter outputs by an amount supposedly equivalent to blood regurgitated.

In five patients in shock there was good correlation between the values obtained by both methods, whereas others, using the high frequency, undamped ballistocardiograph, have obtained results not in agreement with results based on the Fick principle. Since the latter itself may give rise to a 25 per cent range of variation the low frequency, critically damped ballistic method promises to be a simple and convenient tool in the determination of cardiac output in normal and abnormal states.

FRIEDLAND.

Pugh, D. G.: The Roentgenologic Diagnosis of Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 22:130 (April 2), 1947.

In many cases the roentgenologic diagnosis of coarctation of the aorta can be made with ease and accuracy. One of the most important diagnostic features consists of notching of the inferior aspects of the posterior portions of the ribs. Occasionally, notching of the ribs is not conspicuous and is easily overlooked. Infrequently no notching of the ribs can be seen in adult patients who have coarctation of the aorta. This is probably explained by the fact that the degree of stenosis is not great and an extensive collateral circulation does not develop, and, as a result, the intercostal arteries will not be sufficiently enlarged to erode the ribs. Notching of the ribs often cannot be seen in children, and for this reason in this age group the roentgenologic diagnosis of coarctation of the aorta sometimes cannot be made.

In coarctation of the aorta the aortic knob is small or absent and there is hypertrophy of the left ventricle. These signs are in no way pathognomonic of coarctation of the aorta but should lead to further investigation. Infrequently the constricted segment of the aorta can be seen in the left anterior oblique view. In older patients who have atheromatous or calcareous changes in the aorta the coarctation may be seen occasionally, but in young patients this is usually impossible.

When notching of the ribs is not present or is not seen, the diagnosis of coarctation of the aorta is dependent on clinical observation. If there is clinical evidence of coarctation of the aorta, angiocardiology can be of assistance in confirming the diagnosis. This method of study is of particular value prior to surgery.

BELLET.

Shick, R. M.: Surgical Treatment of Coarctation of the Aorta; Report of a Case. Proc. Staff Meet., Mayo Clin. 22:127 (April 2), 1947.

The author presents a preliminary report of a case in which coarctation of the aorta was successfully treated by surgical correction of the malformation. A white man, 34 years of age was referred to the Clinic for consideration of sympathectomy. During the five months prior to his admission, blood pressure readings had varied between 250/125 and 210/95. On the basis of clinical and laboratory findings a diagnosis of coarctation of the aorta with probable high-grade stenosis was made and surgical exploration was carried out. The technique of the operation, described in a subsequent article, resembles in its main features that described by Crafoord and Gross. The postoperative course was uneventful. No anticoagulant therapy was given at any time. The patient was gotten out of bed gradually after the eleventh postoperative day and was dismissed from the hospital on the twenty-second postoperative day.

At the termination of the operation the blood pressure was 164/86 in the right arm and 166/120 in the right leg. At the time of dismissal the values in the right arm varied between 162/90 and 146/76.

BELLET.

Poppe J. K. and de Oliveira, H. R.: Treatment of Syphilitic Aneurysms by Cellophane Wrapping. J. Thoracic Surg. 15:186 (June), 1946.

The authors report a case of a 36-year-old colored man who was admitted to the hospital with a history of syphilis. A large pulsating aneurysm was discovered immediately below the arch of the aorta in the left posterior mediastinum. The blood pressure on the right was 98/66 and on the left, 104/70. No murmurs or thrills were heard over the patient's chest. An exploratory thoracotomy was performed through a posterolateral incision with the resection of the sixth rib. A large pulsating fusiform aneurysm was found involving about one-third of the descending aorta, centering opposite the seventh vertebra. The aneurysmal sac was exposed over about 80 per cent of its surface. A single layer of 1.5 millimeter polythene cellophane was tacked loosely over the exposed areas of the aneurysm. The left lung was then re-expanded, the chest wall closed, and the excess air aspirated from the left pleural cavity. The postoperative course was uneventful with a return of the patient's temperature to normal on the fifth postoperative day. The patient was ambulatory and afebrile at the time of discharge on the thirteenth postoperative day, complaining only of a continued pain in the left side of the posterior part of the chest. This pain was gradually

decreased, and the throbbing ache in the left side of the anterior part of the chest completely disappeared during the first three months after his operation.

The use of polythene cellophane seems to offer a successful method of producing gradual fibrosis and obliteration of aneurysms and large vessels; the experimental studies reported here have shown that, in order to obtain the desired result, it is necessary to use a particular type of cellophane, since some varieties produce no fibrosis. Polythene cellophane has been found useful not only in the treatment of aortic aneurysms but also in the obliteration of a patent ductus arteriosus.

BELLET.

Govea, J.: Ayerza's Disease. *Rev. cubana de cardiología*. 7:145 (July), 1946.

As a result of his personal experience and that of the Argentine school, the author reaffirms his belief in the existence of Ayerza's disease as a distinct nosologic entity. Profound cyanosis and chronic right heart failure, preceded by a history of chronic cough, are the outstanding features of the disease. Contrary to general belief, syphilis is absent as often as it is present.

The fundamental physiologic disturbance is in the alveolar gaseous exchange. The "black cardiac" utilizes only 47 per cent of the tidal air, in contrast to the normal 73 per cent, with which to aerate the pulmonary alveoli. The alveolar oxygen tension is reduced to 10 per cent or less with a corresponding rise in alveolar and blood carbon dioxide. A compensatory polycythemia develops and deep cyanosis results. Alveolar hypoventilation is the basic physiologic disturbance of Ayerza's disease.

Anatomically, the bronchopulmonary lesions and pulmonary artery sclerosis result in hypertension of the lesser circulation with secondary right ventricular hypertrophy and failure. Right axis deviation is present in the electrocardiogram and at times a pattern suggestive of posterior or right coronary insufficiency can be seen. These patients often complain of typical anginal pain which may be related to acute right ventricular dilatation. However, the anoxemia, carbon dioxide acidosis, and increased parasympathetic tone present in these patients are the most likely causes of the coronary pain. Finally, some of these patients do not die as a result of chronic right heart failure but of sudden cardiac asystole. This, according to the author, is worthy of emphasis because it occurs often unexpectedly in cases that are fairly well under control.

GOLD.

Cossio P., and Berconsky, I.: Acute Benign Pericarditis. *Medicina* 7: 1 (Feb.), 1947.

The authors report ten cases of acute, benign (non-suppurative) pericarditis of unknown origin. This condition began suddenly in otherwise healthy adults, who manifested substernal or precordial pain that radiated to the shoulders, neck, arms, or abdomen, and was aggravated by deep breathing, cough, or movements of the trunk. Additional manifestations were moderate fever, leucocytosis, and increased sedimentation rate. The cardinal sign was a to-and-fro pericardial friction rub which was followed in 30 per cent of the cases by pericardial effusion that did not require aspiration. The illness usually lasted from two to six weeks. Recurrence of precordial pain occurred in some cases. The electrocardiographic pattern was diagnostic. It consisted of elevation of the S-T segment in all leads, followed by inversion of the T waves. Complete restitution to normal occurred in all cases. The authors distinguish this disease from suppurative pericarditis, tuberculosis pericarditis, myocardial infarction with and without pericarditis, and spontaneous mediastinal emphysema.

GOLD.

Castellanos A., Perez De Los Reyes, R., and Garcia Lopez, A.: Angiocardiography—Comparative Study With Autopsy Findings. *Rev. cubana de Cardiología*. 8:29 (Feb.), 1947.

The authors who originated angiocardiography in the study of congenital lesions (the dextro-angiocardiogram) compared their x-ray diagnosis with the autopsy findings in twenty-three subjects and found that an exact anatomic diagnosis was made in twelve cases, or 52.1 per cent; while a partial diagnosis was made in nine cases, or 39.1 per cent. In the remaining two cases the lesions

were misdiagnosed. With the further extension of this diagnostic procedure by Steinberg and Robb (levoangiocardigram), the chances of correct diagnosis of anatomic defects of the heart have been greatly increased.

GOLD.

Bell, F. K., Carr, C. J., and Krantz, J. C.: Digitalis V. The Baljet Reaction and Pharmacodynamics of Diginin. J. Pharmacol. & Exper. Therap. 89:143 (Feb.), 1947.

In 1937, Karrer isolated a new glycoside from the leaves of *Digitalis purpurea* called diginin. It differs from the other glycosides in that it is not a lactone. It was reported as having little cardiotonic activity. Its presence, in significant amounts, appeared to be an obstacle to the assay of digitalis preparations by the colorimetric method based upon the Baljet reaction (glycosides, in the presence of an excess alkaline sodium picrate, develop a red color). Hagemeyer reported a high color intensity for diginin. Solutions of diginin in absolute methanol were tested in concentrations of from 5 to 30 mg. per 100 cubic centimeters. They showed low color values when compared to digitoxin on either a weight or a molar basis. Plotted on a basis of molar concentration, diginin gave colorimetric readings approximately one-third those of digitoxin.

The significance of diginin in standard preparations, bioassayed by the Baljet reaction, is limited. It must be assumed that the U. S. P. preparations contain significant amounts of this glycoside. When unknowns are compared to U. S. P. standards, it would take a large discrepancy of diginin content to cause a significant error. Diginin was found to have very little cardiotonic action in both cats and dogs. Large quantities (ten times more than digitoxin) were necessary to cause death.

GODFREY.

Kissane, R. W., Fidler, R. S., and Clark, T. E.: Liver Dysfunction in Rheumatic Heart Disease. Preliminary Report. Am. J. M. Sc. 213:410 (April), 1947.

The cephalin-cholesterol flocculation reaction was found positive in 72 per cent of 136 cases of rheumatic heart disease. Neither the valvular lesion, age of the patient, nor the length of time rheumatic heart disease had existed seemed to effect any variation from the percentage of positives in the entire group. Also, there was no correlation between the degree of positive reaction and the degree of functional severity of rheumatic heart disease.

DURANT.

Blumberg, N., and Schloss E. M.: The Effect of Circulatory Factors on the Bromsulphalein Test in Liver Disease. Am. J. M. Sc. 213:470 (April), 1947.

Evidence is presented that two factors may be concerned in the mechanism of bromsulphalein retention: hepatic excretory dysfunction, and circulatory inadequacy. There does not appear to be any present method for delineating the proportion of influence to be assigned to each factor where both are operative in the same patient. However, the data suggest the advisability of performing studies of circulatory integrity in those cases of liver disease in which there is clinical evidence of concomitant cardiovascular involvement. While it is evident that those instances in which such circulatory studies are abnormal will fail to indicate the proportion of abnormal dye retention due to either factor, it is equally true that those in which circulation time and venous pressure are normal will present confirmation that the abnormal bromsulphalein retention can then be attributed solely to hepatic dysfunction.

DURANT.

Hirsch, H. L., Rotman-Kavka, G., Dowling, H. F., and Sweet, L. K.: Penicillin Therapy of Scarlet Fever. J.A.M.A. 133:657 (March 8), 1947.

These authors treated eighty-six patients with scarlet fever with penicillin X, crystalline penicillin G and commercial penicillin. The first thirty-four patients were treated with penicillin X and five patients were treated with penicillin G. Thereafter, alternate patients were given either commercial penicillin in doses of 25,000 units every 3 hours, or 9,000 to 27,000 units of antitoxin,

depending on the degree of toxicity. A group of eighteen patients received oral penicillin in a dose of 125,000 units every three hours. These authors established five days as a minimum period of treatment for scarlet fever.

Penicillin therapy resulted in a prompt fall in temperature, a decrease in toxicity, a decided reduction in the incidence of pyogenic complications, and practically eliminated the carrier state. Penicillin was more effective than antitoxin or symptomatic therapy in the prevention of complications and in reducing the number of carriers and was equally effective in decreasing toxicity. Antitoxin caused a more rapid decline in temperature than did penicillin. However, temperature dropped more rapidly in patients given penicillin than in symptomatically-treated patients.

These authors feel that a further advantage of penicillin over antitoxin in the routine treatment of scarlet fever is the elimination of the frequent occurrence of serum sickness following the use of antitoxin. They also state that severely toxic patients should receive antitoxin in addition to penicillin.

BELLET.

Levine, S. A., and Geremia, A. E.: Clinical Features of Patent Ductus Arteriosus With Special Reference to Cardiac Murmurs. Am. J. M. Sc. 213:385 (April), 1947.

The accurate diagnosis of congenital heart disease is no longer a purely academic or intellectual endeavor now that modern surgery has made possible the successful treatment of certain types of such disease. Realizing this fact, the authors have made a very thorough study of thirty-seven verified cases of patent ductus arteriosus, with special emphasis on the auscultatory findings before and after operation.

The first interest was the intensity of the murmur. In twenty-five patients in whom accurate estimation by a competent observer was made preoperatively, the average intensity of the systolic component was found to be Grade 4; in eleven, Grade 3; and in one, Grade 2. In twenty-one instances the intensity of the diastolic component was carefully noted preoperatively and the average was found to be Grade 3. In no instance was the diastolic component louder than the systolic. In five patients it was faint enough to be called Grade 2, and in one instance it was considered to be only Grade 1.

There was no instance in the series in which no murmur could be heard at all, although in one instance it disappeared during the last month before death. The murmur was generally loudest in the pulmonary area. When very loud it was widely distributed, being heard in the interscapular area and even, at times, as far down the arm as the olecranon process. Apical systolic murmurs were always present, and in some patients the continuous systolic and diastolic murmur were also heard, though fainter, at the apex. In four patients a definite mid-diastolic murmur, unlike the pulmonic murmur and resembling the murmur of mitral stenosis, was heard. A definite palpable systolic thrill was present in twenty-one of the thirty-seven cases, and was maximal in the second and, occasionally, in the first left intercostal space. It was always systolic in time but occasionally extended well into diastole.

The most significant observation in the postoperative study was the fact that a slight pulmonic systolic murmur may persist for a considerable time after successful division of the ductus. Such basal systolic murmurs may possibly be explained on the basis of continued dilatation of the pulmonary artery, or may have the same debatable significance ascribed to other inconsequential or functional basal systolic murmurs. The occasional persistence of a basal systolic and diastolic murmur may be interpreted in one of several ways: namely, recanalization of the duct (when it has been ligated but not divided), the presence of bacterial endocarditis of the aortic valve, or an additional anatomic lesion, such as coarctation of the aorta or some other congenital abnormality.

A review of the blood pressure readings confirmed the fact that the pulse pressure is increased in patent ductus arteriosus and that the levels return to normal after treatment. The average systolic pressure was not altered by operation, but the average diastolic pressure rose 20 millimeters of mercury.

In the thirty-four cases in which preoperative electrocardiograms were available, four showed left axis deviation; only one showed right axis deviation. The electrocardiogram, therefore, proved to be indirectly helpful in diagnosis since right axis deviation is very common in various other forms of congenital heart disease.

The diagnostic problem in exceptional cases may be very difficult. In these, catheterization of the heart is necessary to establish an accurate and definitive preoperative diagnosis. Only in this way will some cases avoid harmful surgery.

DURANT.

Smith, B. C., and Quimby, E. H.: The Use of Radioactive Sodium in the Study of Peripheral Vascular Disease. Ann. Surg. 125:360 (March), 1947.

By means of an intravenous injection of 3 to 7 cc. of a sterile solution of radioactive sodium and counting the arrival of the radioactive atoms at the sole of the foot by a Geiger-Müller counter, the authors have developed a method of studying the circulation to an extremity. The radioactive sodium leaves the capillaries, enters the extravascular fluid, and builds up to an equilibrium, and curves can be plotted which have a definite normal range.

Various pathologic states, such as occlusive vascular disease on an arteriosclerotic and also on a thrombangiitic basis, have been studied. The test enabled the authors to determine the advisability of conservative therapy, and if amputation became necessary, the lowest possible level in which it was safe.

The test also may be of value in the preoperative selection of hypertensive patients for thoracolumbar sympathectomy. Patients whose curves were very low, that is, with a considerable spasmodic element, usually benefitted greatly, whereas those with normal curves either experienced a severe vascular complication or died following operation.

LORD.

Saccommanno, G., Utgterback, R. A., and Klemme, R. M.: Anatomic Data Regarding the Surgical Treatment of Angina Pectoris. Ann. Surg. 125:49 (Jan.), 1947.

Employing dogs as their experimental animal, the authors isolated the spinal cord between the eighth cervical and the seventh thoracic segments. The spinal nerves were also isolated and cut between a ligature and the cord. The effect of stimulation of each spinal nerve on the pulse rate and blood pressure was studied. They observed that cardiac acceleration was greatest when the second and third thoracic nerves were stimulated; acceleration was present but less in degree when the fourth and fifth nerves were stimulated. There was no change in rate on stimulation of the eighth cervical and first thoracic nerves. The authors also observed that elevation of the blood pressure followed stimulation of the second through the seventh thoracic nerves, in a relatively constant manner.

As a result of their experimental data and that of others, they concluded that surgical removal or alcohol injection of the second, third, and fourth thoracic sympathetic ganglia on the left side (usually the affected side) will result in relief of anginal pain and bring about diminution of coronary spasm.

LORD.

Southworth, J. L. and Russek, H. I.: A Technic for Testing Hypertensive Patients Preoperatively. Ann. Surg. 125:119 (Jan.), 1947.

The authors first point out that sympathectomy in the treatment of hypertensive patients is a worthwhile procedure. The mechanism by which operation brings relief is obscure but seems to be most valuable in those patients who demonstrate a significant degree of vasospasm. The most difficult task has been the proper selection of cases preoperatively, and they believe that continuous caudal analgesia and lumbar peridural anesthesia have real value in determining which patient will have effective blood pressure reduction following sympathectomy. The technic of continuous caudal analgesia is simpler than lumbar peridural anesthesia, but the latter more nearly reproduces the denervation achieved by thoracolumbar sympathectomy.

Approximately one third of the paper is devoted to a description of the two technics. No results are offered as these have been presented in an earlier report.

LORD.

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

The Chairman of the Program Committee for the Annual Scientific Session is Dr. Herrman L. Blumgart, 330 Brookline Avenue, Boston, Massachusetts. All who desire to present papers at the meetings in Chicago on June 18 and 19 should forward to Dr. Blumgart an abstract of the proposed presentation of not more than 500 words. The dead line for the receipt of abstracts is Feb. 1, 1948.

MEMBERSHIP

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members residing in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....	\$ 2.50	Contributing Membership.....	\$25.00
Journal Membership.....	\$10.00	Patron Membership.....	\$50.00 or more

The dues of the local Heart Associations are added to these.

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*.

Journal Membership includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the AMERICAN HEART JOURNAL through the publishers does not provide for membership in the American Heart Association, except as provided for in a Journal Membership.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

OFFICERS

President
DR. ARLIE R. BARNES

Treasurer
SAMUEL HARRELL

President Elect
DR. TINSLEY R. HARRISON

Secretary
DR. HARRY E. UNGERLEIDER

Medical Director
DR. CHARLES A. R. CONNOR

Vice-President
DR. CARL J. WIGGERS

Executive Secretary
DR. H. M. MARVIN

BOARD OF DIRECTORS

*THOMAS I. PARKINSON, Chairman..... New York City
DR. EDGAR V. ALLEN..... Rochester, Minn.
*DR. E. COWLES ANDRUS..... Baltimore
*DR. ARLIE R. BARNES..... Rochester, Minn.
DR. WILLIAM H. BUNN..... Youngstown, Ohio
*DR. GEORGE E. BURCH..... New Orleans
*S. DEWITT CLOUGH..... Chicago
*COLGATE W. DARDEN, JR..... Charlottesville, Va.
*JUSTIN DART..... Los Angeles
DR. CLARENCE E. DE LA CHAPELLE..... New York City
DR. GEORGE K. FENN..... Chicago
DR. MORRIS FISHBEIN..... Chicago
RUDOLPH F. HAFFENREFFER..... Providence
*SAMUEL HARRELL..... Indianapolis
*DR. TINSLEY R. HARRISON..... Dallas
ALFRED C. HOWELL..... Bethel, Conn.
*DR. T. DUCKETT JONES..... Boston
DR. LOUIS N. KATZ..... Chicago

DR. JOHN D. KEITH..... Toronto, Can.
DR. ROBERT L. KING..... Seattle
MRS. WENDELL KINNEY..... Los Angeles
DR. WILLIAM B. KOUNTZ..... St. Louis
DR. EUGENE M. LANDIS..... Boston
DR. ROBERT L. LEVY..... New York City
DR. H. M. MARVIN..... New Haven, Conn.
DR. THOMAS M. McMILLAN..... Philadelphia
*ROBERT L. MEHORNAY..... Kansas City, Mo.
*DR. IRVINE H. PAGE..... Cleveland
*DR. JOHN J. SAMPSON..... San Francisco
DR. HOWARD B. SPRAGUE..... Boston
DR. EUGENE A. STEAD, JR..... Durham, N. C.
DR. J. ROSS VEAL..... Washington, D. C.
DR. HARRY E. UNGERLEIDER..... New York City
DR. HOWARD F. WEST..... Los Angeles
DR. CARL J. WIGGERS..... Cleveland
*DR. IRVING S. WRIGHT..... New York City

*Executive Committee.

ASSEMBLY

DR. EDGAR V. ALLEN..... Rochester, Minn.
JAMES ANDERSON..... Philadelphia
DR. E. COWLES ANDRUS..... Baltimore
DR. GRAHAM ASHER..... Kansas City, Mo.
DR. ARLIE R. BARNES..... Rochester, Minn.
DR. EMMET B. BAY..... Chicago
DR. ALFRED BLALOCK..... Baltimore
ALVA BRADLEY..... Cleveland
EARLE BROWN..... Minneapolis
DR. LEWIS T. BULLOCK..... Los Angeles
DR. WILLIAM H. BUNN..... Youngstown, Ohio
DR. GEORGE E. BURCH..... New Orleans
DR. EDWARD W. CANNADY..... East St. Louis, Ill.
HARRY C. CARR..... Philadelphia
DR. FRANCIS L. CHAMBERLAIN..... San Francisco
PAUL F. CLARK..... Boston
S. DEWITT CLOUGH..... Chicago
DR. WARREN B. COOKSEY..... Detroit
CHANNING H. COX..... Boston
JAMES A. CUNNINGHAM..... Chicago
COLGATE W. DARDEN, JR..... Charlottesville, Va.
JUSTIN DART..... Los Angeles
DR. CLARENCE E. DE LA CHAPELLE..... New York City
DR. GEZA DE TAKATS..... Chicago
DR. FRANCIS R. DIEUAIDE..... New York City
DR. HARVEY M. EWING..... Montclair, N. J.
DR. GEORGE K. FENN..... Chicago
RICHARD J. FINNEGAN..... Chicago
DR. MORRIS FISHBEIN..... Chicago
DR. NORMAN E. FREEMAN..... San Francisco
ARTEMUS L. GATES..... New York City
SAMUEL GOLDWYN..... Los Angeles
A. E. GRAUER..... Vancouver, B. C., Can.
DR. JAMES A. GREENE..... Houston
RUDOLPH F. HAFFENREFFER..... Providence
SAMUEL HARRELL..... Indianapolis
RICHARD F. HARRISON..... Syracuse, N. Y.
DR. TINSLEY R. HARRISON..... Dallas
DR. JOHN HEPBURN..... Toronto, Can.
DR. GEORGE R. HERRMANN..... Galveston
DR. J. G. FRED HISS..... Syracuse, N. Y.
ALFRED C. HOWELL..... Bethel, Conn.
DR. W. C. HUEPER..... New York City
COLEMAN JENNINGS..... Washington, D. C.
DR. T. DUCKETT JONES..... Boston
DR. ALBERT D. KAISER..... Rochester, N. Y.
DR. LOUIS N. KATZ..... Chicago
SAMUEL H. KAUFFMANN..... Washington, D. C.
DR. JEROME G. KAUFMAN..... Newark, N. J.
DR. JOHN D. KEITH..... Toronto, Can.
DR. ROBERT L. KING..... Seattle
MRS. WENDELL KINNEY..... Los Angeles
DR. WILLIAM B. KOUNTZ..... St. Louis
DR. CHESTER M. KURTZ..... Madison, Wis.
DR. EUGENE M. LANDIS..... Boston

DR. BERNARD W. LEONARD..... Washington, D. C.
DR. ROBERT L. LEVY..... New York City
CLARE BOOTHE LUCE..... Ridgefield, Conn.
DR. HAROLD C. LUETH..... Omaha
RUTH E. LYNCH..... Los Angeles
DR. LOUIS E. MARTIN..... Los Angeles
DR. H. M. MARVIN..... New Haven, Conn.
DR. EDWIN P. MAYNARD, JR..... Brooklyn
DR. SAMUEL J. McCLENDON..... San Diego
ALFRED J. MCCOSKER..... New York City
DR. HUGH MCCULLOCK..... St. Louis
DR. JOHNSON MCGUIRE..... Cincinnati
DR. THOMAS M. McMILLAN..... Philadelphia
ROBERT L. MEHORNAY..... Kansas City, Mo.
DR. J. ROSCOE MILLER..... Chicago
RICHARD M. MOSS..... Belleville, Ill.
DR. E. STERLING NICHOL..... Miami
DR. FRANKLIN R. NUZUM..... Santa Barbara, Calif.
DR. IRVINE H. PAGE..... Cleveland
THOMAS I. PARKINSON..... New York City
DR. MYRON PRINZMETAL..... Los Angeles
DR. SAMUEL PROGER..... Boston
DR. DICKINSON W. RICHARDS, JR..... New York City
DR. HAROLD H. ROSENBLUM..... San Francisco
DR. PHILIP ROSENBLUM..... Chicago
DR. HOMER P. RUSH..... Portland, Ore.
DR. JOHN J. SAMPSON..... San Francisco
DR. FRANCIS T. SCHWENTKER..... Baltimore
DR. HAROLD N. SEGALL..... Montreal, Can.
DR. ARTHUR SELZER..... San Francisco
DR. M. J. SHAPIRO..... Minneapolis
DR. HOWARD B. SPRAGUE..... Boston
DR. ISAAC STARR..... Philadelphia
HAROLD E. STASSEN..... St. Paul
DR. EUGENE A. STEAD, JR..... Durham, N. C.
DR. ERNEST L. STEBBINS..... Baltimore
DR. WILLIAM D. STROUD..... Philadelphia
DR. HOMER F. SWIFT..... New York City
DR. ALEXANDER W. TERRELL..... Dallas
DR. WILLIAM P. THOMPSON..... Los Angeles
DR. HARRY E. UNGERLEIDER..... New York City
DR. J. ROSS VEAL..... Washington, D. C.
DR. LOUIS E. VIKO..... Salt Lake City
DR. MAURICE VISSCHER..... Minneapolis
JOE E. WERTHAN..... Nashville
DR. HOWARD F. WEST..... Los Angeles
DR. PAUL D. WHITE..... Boston
CARL WHITMORE..... New York City
DR. CARL J. WIGGERS..... Cleveland
DR. FRANK N. WILSON..... Ann Arbor
DR. J. EDWIN WOOD, JR..... Charlottesville, Va.
GUS S. WORTHAM..... Houston
DR. IRVING S. WRIGHT..... New York City
J. D. ZELLERRACH..... San Francisco

American Heart Journal

Vol. 34

NOVEMBER, 1947

No. 5

Original Communications

HIGH T WAVES IN THE EARLIEST STAGE OF MYOCARDIAL INFARCTION

WILLIAM DRESSLER, M.D., NEW YORK, N. Y., AND
HUGO ROESLER, M.D., PHILADELPHIA, PA.

HIGH T waves are known to occur in the limb and chest leads in the healing stage of myocardial infarction.¹⁻⁴ The early investigators of the electrocardiographic changes in myocardial infarction mentioned also the development of high T waves immediately following coronary occlusion. Smith⁵ noted, immediately after ligation of a coronary branch in the experimental animal, an increase of the amplitude of the T wave proportionate to the size of the ligated artery. When a large artery was occluded, the T wave became tall and exceeded the height of the R deflection. Within twenty-four hours the large T wave became sharply inverted. Pardee,⁶ in his first report on the electrocardiogram in myocardial infarction, stated that records taken shortly after obstruction of a coronary branch may have as typical features "the extreme height of the T wave and the fact that this wave starts from a point of the QRS group well away from the base line." Later investigators^{4,7-10} failed to describe high T waves as an early feature in myocardial infarction, possibly because they were more impressed with the elevation of S-T, or perhaps because the overwhelming number of clinical investigations dealt primarily with subacute stages of infarction. Nor are high T waves as an early sign of infarction mentioned by the majority of current cardiologic textbooks.¹¹⁻¹⁴ Bohning and Katz³ have reported "transient elevation of the T wave" in a few cases in which the clinical picture was suspicious of coronary occlusion.

We have observed cases in which high T waves were the outstanding feature in the earliest stage of myocardial infarction, when elevation of S-T and signifi-

From the Department of Medicine, Israel Zion Division, Maimonides Hospital, Brooklyn, N. Y., and the Departments of Medicine and Radiology, Temple University Hospital and Medical School, Philadelphia, Pa.

Received for publication Feb. 18, 1947.

cant changes of QRS were absent. Such observations prompted our study, which is the subject of this report. It includes twenty-seven instances of recent myocardial infarction which were observed in twenty-four patients. In all cases early electrocardiograms were taken, some as early as one and one-quarter hours and none later than twelve hours after the beginning of the attack. In all but two cases follow-up tracings were obtained. In thirteen instances serial records were made daily or at intervals of several hours.

CASE REPORTS

CASE 1.—J. B. was a 58-year-old man. While working on May 8, 1944, he experienced severe pain in the left side of the chest and in the left arm and almost fainted. The pain lasted for several hours and was not quite relieved by morphine. The attack was followed by low-grade fever and increase of the white blood count and sedimentation rate.

The first electrocardiogram (Fig. 1, A) was taken three and one-half hours after the onset of symptoms. In Lead I the amplitude of the upright T is 3.5 mm.; there is no elevation of the S-T junction. Lead CF₄ (the only chest lead taken at the first examination) shows a small Q, a rather high R deflection, and a conspicuous S wave. The S-T junction is 2.2 mm. above the base line; the amplitude of the T deflection is 20 millimeters.

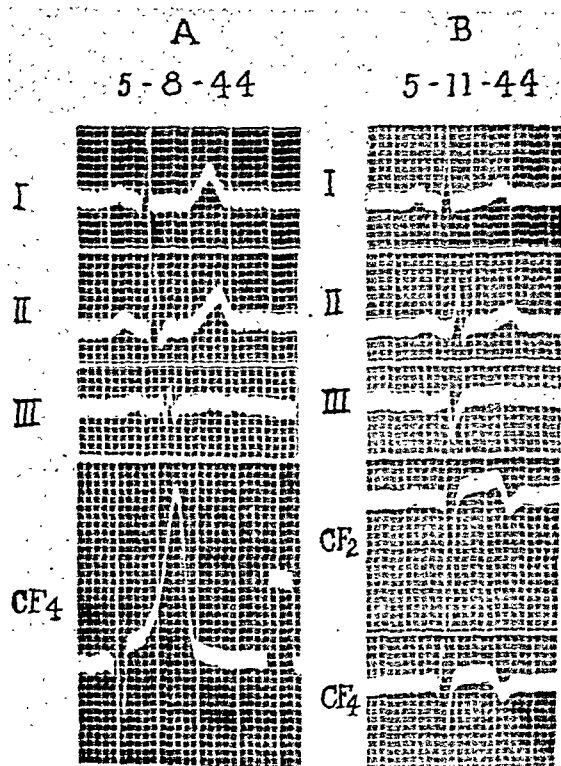


Fig. 1.—Case 1. Signs diagnostic of anteroseptal infarction. Tracing A, taken three and one-half hours after the onset of symptoms, shows high T waves in Leads I and CF₄, without abnormal elevation of S-T or significant changes of QRS. B, Three days after the coronary attack. The chest leads show significant changes of QRS and inversion of T.

The second electrocardiogram (Fig. 1, B) was taken three days after the attack. It shows marked decrease of the amplitude of the T waves. A deep QS deflection is present in Lead CF₄. The amplitude of R has decreased in Lead CR₁. In both chest leads the T wave is mainly inverted.

Summary.—An electrocardiogram taken three days after a coronary attack was diagnostic of anteroseptal infarction. In the first electrocardiogram, which was obtained three and one-half hours after the onset of symptoms, high T waves in the limb leads and especially in the chest lead were the outstanding diagnostic feature. In this early stage significant changes of QRS and abnormal elevation of S-T were absent.

CASE 2.—H. L., a 50-year-old man, had suffered from hypertension for many years. On Sept. 22, 1939, while playing cards, he was seized with severe precordial pain which radiated to the left shoulder and arm and caused him to perspire profusely. On the next day the blood pressure was 90/70 and the white blood count was 13,800.

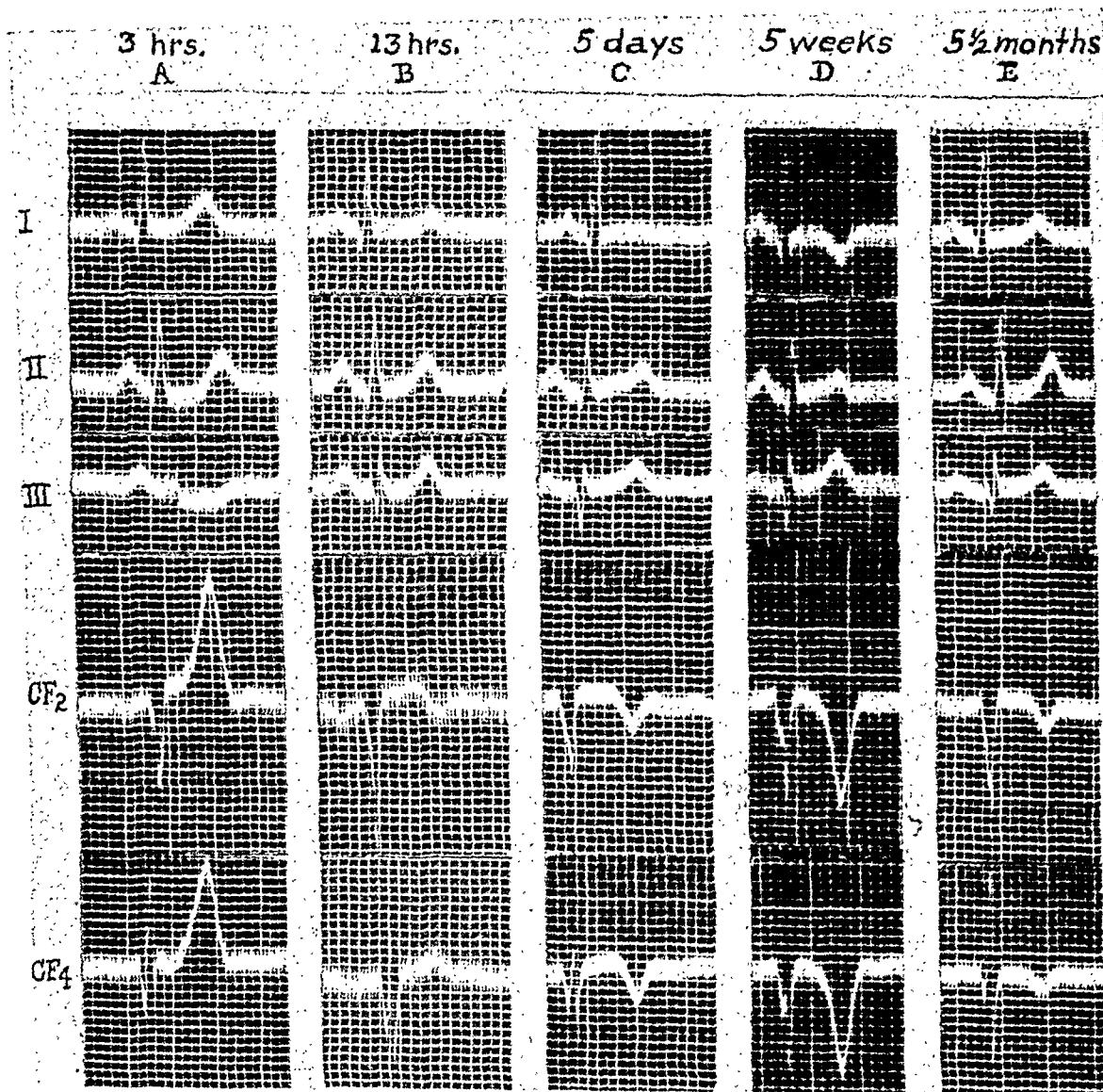


Fig. 2.—Case 2. Signs diagnostic of anteroseptal infarction. Tracing A, taken three hours after the onset of symptoms, shows, in addition to significant Q waves in the chest leads, high T waves in Lead I and especially in the chest leads without significant elevation of S-T. B, C, and D show inversion of the high T waves. E shows regressive changes.

The first electrocardiogram (Fig. 2, A) was taken three hours after the onset of symptoms. It shows marked depression of S-T in Leads II and III, but no significant elevation of S-T in Lead I. The amplitude of T_1 is 3 millimeters. Lead CF_2 shows a deep QS deflection and Lead CF_4 ,

a significant Q wave. In both chest leads the T waves are usually high; their amplitude is 14 mm. in Lead CF₂ and 12 mm. in Lead CF₄. The high T waves are not associated with significant elevation of S-T.

The second electrocardiogram (Fig. 2, B), which was taken thirteen hours after the onset of symptoms, shows marked decrease in the amplitude of T in Lead I and in the chest leads. In Lead CF₂ the T wave is semi-inverted. The next two tracings (C and D) which were taken five days and five weeks, respectively, after the onset of symptoms, show complete inversion of T in Lead I and in the chest leads. In tracing E, which was obtained five and one-half months after the attack, regressive changes of T are noted.

Summary.—The electrocardiograms were diagnostic of anteroseptal infarction. In the early stage of infarction, three hours after the onset of symptoms, high T waves were noted in Lead I and especially in the chest leads; they were no longer present thirteen hours after the beginning of the attack. The high T waves were not associated with abnormal elevation of S-T.

CASE 4.—L. C., was a 36-year-old man. In the latter part of November, 1945, he suddenly felt as though he had been "hit in the epigastric notch." Three weeks later, while working, he had what he considered to be indigestion; again there was distress in the epigastric region. Similar attacks occurred more often during the first two weeks of March and were not related to intake of food. They lasted from ten to fifteen minutes. At 2 P.M. on March 14, 1946, the patient experienced a burning sensation in the epigastrium and perspired profusely. He vomited and felt weak. When he was brought to the accident dispensary, he still complained of a pressing and burning sensation behind the sternum. The blood pressure was 90/70. The white blood count was 17,100. The sedimentation rate was normal. On the next day the temperature rose and remained above normal for nine days. The sedimentation rate was elevated on the fourth day after the attack.

The first electrocardiogram (Fig. 3, A) was taken three hours after the onset of symptoms. It shows high T waves in Lead I and especially in the chest leads. Instead of elevation, marked depression and upward concavity of S-T is noted, notably in Leads CR₃ through CR₆. No significant changes in QRS are present.

Fig. 3, B, was taken eighteen hours after the onset of symptoms. It shows marked decrease of the amplitude of R and T in all leads except Leads II and III. A significant Q wave is present in Leads I and CR₁. The R deflection is very small in Leads CR₁ through CR₄. Elevation of S-T is noted where depression was previously present. The T wave is semi-inverted in Leads I and CR₂ through CR₄.

Three days after the attack (Fig. 3, C) inversion of T is noted in all leads except Leads II, III, and CF₁. A week after the attack (Fig. 3, D) inversion of T is more pronounced while elevation of S-T is regressive.

Summary.—The electrocardiograms were diagnostic of anteroseptal infarction. In the earliest stage, three hours after the onset of symptoms, unusual electrocardiographic changes were observed: marked depression of S-T associated with abnormally high T waves in Lead I and in the chest leads. Significant changes of QRS did not appear until eighteen hours after the onset of symptoms, when depression of S-T was replaced by elevation, and the high T waves were decreased in amplitude and became semi-inverted.

CASE 15.—M. N. was a 42-year-old man. On June 16, 1944, while convalescing from pleuropneumonia, he was suddenly seized with severe pressing pain across his chest which radiated to the left arm. He was nauseated and vomited. The attack was followed by a rise in temperature and increase of the sedimentation rate.

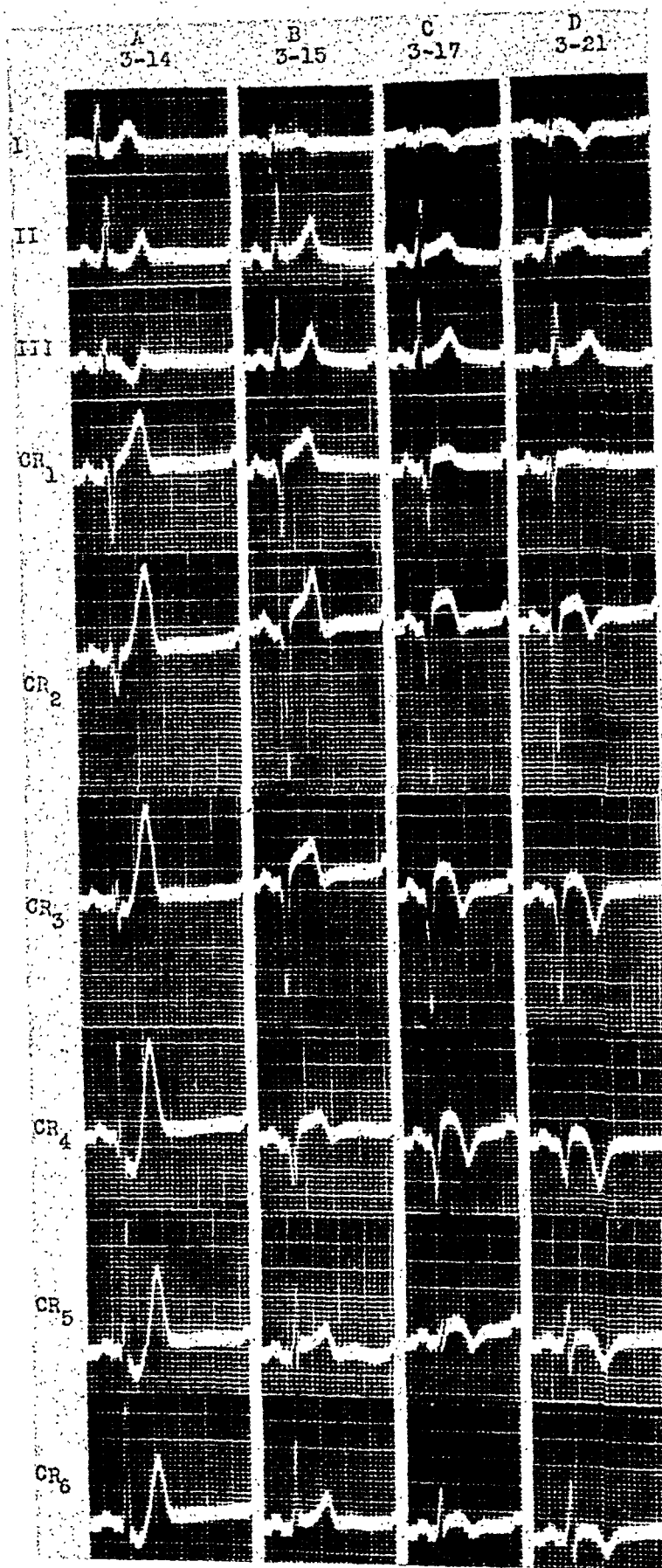


Fig. 3.—Case 4. Signs diagnostic of anteroseptal infarction. Tracing A, obtained three hours after the onset of the attack, shows high T waves in Lead I and in the chest leads associated with abnormal depression of S-T; this is especially distinct in Leads CR₃ through CR₆. Significant changes in QRS were not present until eighteen hours after the onset of symptoms (tracing B), when the high T waves had decreased in amplitude and become semi-inverted. C and D, Progressive inversion of the previously high T waves.

The first electrocardiogram (Fig. 4, *A*) was taken on the day of the attack. It shows an insignificant Q wave in Leads I and II, and an S deflection in Lead III. The S-T junction is depressed in Lead I and slightly elevated in Lead III. T_1 is inverted and T_3 is upright; its amplitude is 4.3 millimeters. The chest leads are normal except that the T wave in Lead CF_4 is of low voltage and notched.

A second tracing (Fig. 4, *B*) was taken three days after the attack. It shows in Leads II and III changes of QRS and T that are characteristic of posterior infarction. The amplitude of T_2 is diminished; T_3 has become inverted. In the chest leads the amplitude of the T waves has increased.

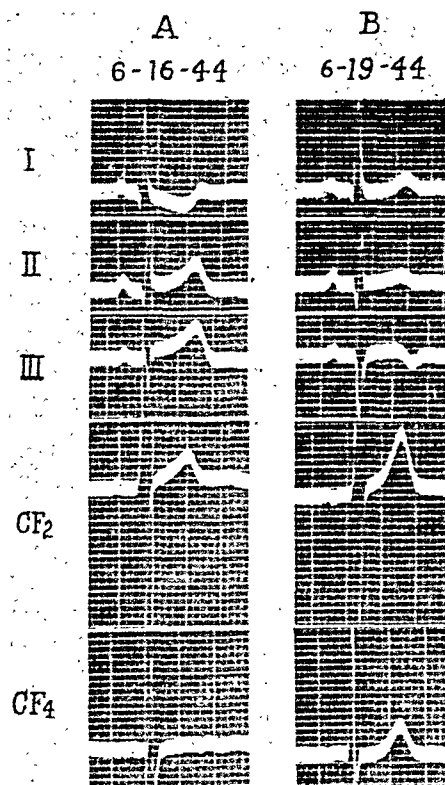


Fig. 4.—Case 15. Signs diagnostic of posterior infarction. Tracing A, obtained on the day of the attack, shows high T waves in Lead III without abnormal elevation of S-T or significant changes of QRS. B, Three days after the coronary attack. Deep Q waves in Leads II and III and inversion of T_3 .

Summary.—The electrocardiograms were diagnostic of posterior wall infarction. The first tracing, which was obtained on the day of the attack, showed unusually high T waves in Lead III without significant elevation of S-T or changes in QRS. Transient change of T in Lead CF_4 was probably due temporary involvement of the lateral wall.

CASE 16.—J. M. was a 70-year-old man. On March 11, 1946, while walking to the hospital to receive treatment for intermittent claudication, he was seized with severe pain in the region of the lower portion of the sternum and in the epigastrium. The pain continued for more than an hour after the patient arrived in the hospital; morphine was then given. The white blood count was 15,200. One day after the attack the temperature rose and remained above normal for three days. The sedimentation rate was increased.

The first electrocardiogram (Fig. 5, A) was obtained two and one-half hours after the onset of symptoms. It shows a high T wave in Lead III; its amplitude is 3 millimeters. The S-T junction is only slightly above the base line in Leads II and III. There is marked depression of S-T and inversion of T in Lead I and in the chest leads. Significant changes of QRS are absent.

Fig. 5, B, was taken three days after the attack. It shows in Leads II and III changes of QRS and T that are characteristic of posterior wall infarction. T₂ and T₃ have become inverted, while in the chest leads the T waves have become upright. There is still slight depression of S-T in the chest leads. In the next tracing (Fig. 5, C), taken nine days after the attack, depression of S-T has disappeared.

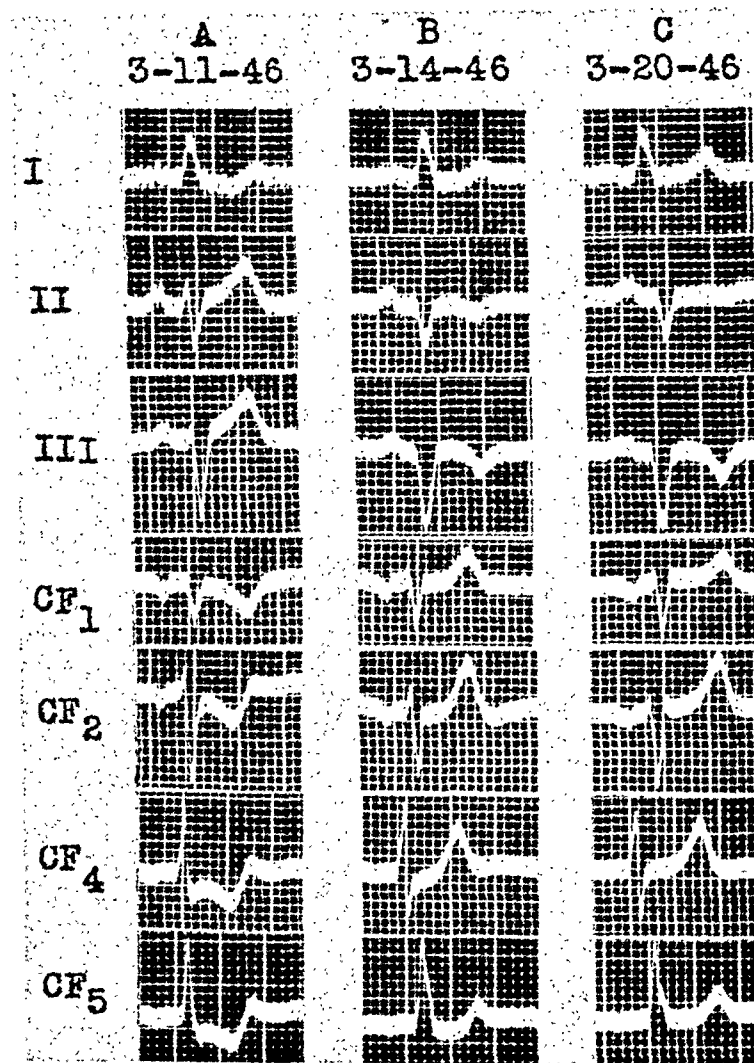


Fig. 5.—Case 16. Signs diagnostic of posterior infarction. Tracing A, obtained two and one-half hours after the onset of the attack, shows, in addition to depression of S-T and inversion of T in Lead I and in the chest leads, high T waves in Leads II and III. The latter are not associated with abnormal elevation of S-T nor with significant changes of QRS. B and C, Deep Q waves and inverted T waves in Leads II and III. Upright T waves in the chest leads.

Summary.—The electrocardiograms were diagnostic of posterior wall infarction. The first tracing, which was obtained two and one-half hours after the onset of symptoms, showed a high T wave in Lead III without significant elevation of S-T or changes in QRS. There were, however, distinct depression of S-T and inversion of T in Lead I and in the chest leads.

CASE 17.—J. T., a 47-year-old man, had suffered from exertional dyspnea for the last five years. While resting on the evening of July 31, 1945, he experienced substernal pain of five minutes' duration. On Aug. 1, 1945, he again felt substernal pain which was accompanied by belching and profuse perspiration. On this occasion the distress lasted for three hours, until relieved by morphine. Then low-grade fever developed and the sedimentation rate was increased.

The first electrocardiogram (Fig. 6, A) was taken two and one-half hours after the onset of symptoms. It shows in Leads II and III high T waves without significant elevation of S-T or changes in QRS. The amplitude of T_2 is 3 millimeters. In the chest leads there is slight depression of S-T.

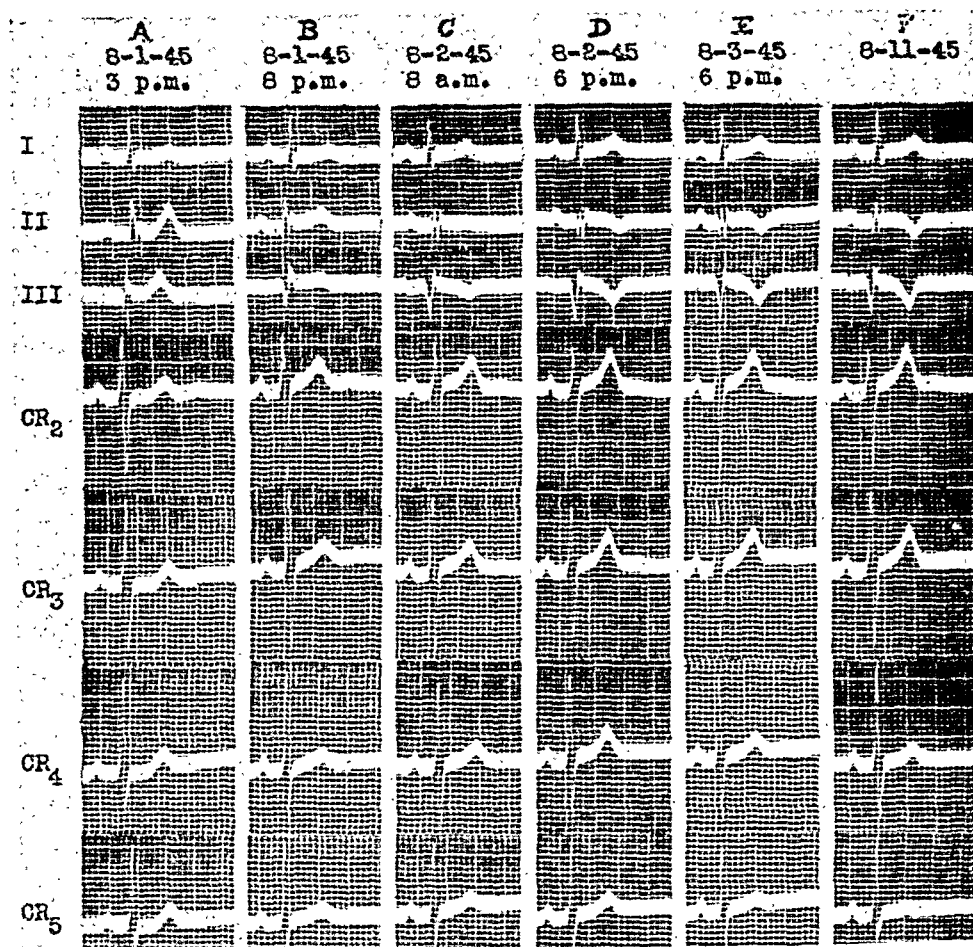


Fig. 6.—Case 17. Signs diagnostic of posterior infarction. Tracing A, obtained two and one-half hours after the onset of symptoms, shows, in addition to slight depression of S-T in Lead I and in the chest leads, high T waves in Leads II and III. The latter are not associated with abnormal elevation of S-T. Significant changes of QRS in Leads II and III did not appear until nineteen hours after the beginning of the attack (tracing C); they developed simultaneously with inversion of T_3 . D, E, and F. Progressive inversion of T_2 and T_3 .

Fig. 6, B, was taken seven hours after the attack. A small Q wave has developed in Lead II, and Q_3 has deepened. The voltage of T_2 and T_3 has markedly decreased.

Fig. 6, C, was taken nineteen hours after the beginning of the attack. Q_3 has broadened and deepened. T_3 has become inverted. In the following tracing (Fig. 6, D), which was obtained twenty-nine hours after the onset of symptoms, significant changes in QRS and inversion of T are noted in Leads II and III. The amplitude of T has increased in Leads CR_2 through CR_4 . E and F of Fig. 6 were taken two days and ten days, respectively, after the attack. Inversion of T_2 and T_3 is even more pronounced. In Lead CR_5 the T wave has become low and diphasic.

Summary.—The electrocardiograms were diagnostic of posterior wall infarction, probably extending to the lateral wall. In the earliest stage, two and one-half hours after the onset of symptoms, the outstanding electrocardiographic feature was high T waves in Leads II and III, not accompanied by abnormal elevation of S-T nor by significant changes of QRS. Slight depression of S-T was noted in the chest leads. It was not until nineteen hours after the beginning of the attack that significant Q waves appeared in Leads II and III, after T₃ had already become inverted.

CASE 23.—F. N. was a 59-year-old man. At 2 p.m. on Sept. 4, 1944, he experienced severe pain across his chest and in both arms. He looked pale and perspired. Morphine was required to relieve the pain. The blood pressure on that day was 190/120. On the following day the white blood count was 16,400 and the sedimentation rate was increased. On Sept. 6, 1944, there was another attack of similar pain which lasted all day long.

The first electrocardiogram (Fig. 7, A) was taken one and one-half hours after the beginning of the first attack of pain. In Leads II and III it shows small Q deflections, marked elevation of S-T, and unusually high T waves. In the chest leads there is marked depression of S-T.

Fig. 7, B, was taken one day after A. In Leads II and III there are significant Q waves and inverted T waves. In the chest leads, the S-T segment is only slightly depressed and the T waves have reached remarkable height, especially in Leads CR₃ and CR₄. In Fig. 7, C, which was obtained two days after A, the leads from the right side of the chest show further increase in the amplitude of T. On the other hand, in Lead CR₅ the S-T segment is somewhat elevated and runs a straight course.

Fig. 7, D, was obtained one day after the second attack of severe chest pain. It shows marked changes in Leads CR₃ through CR₅; the S-T segment is abnormally elevated and the amplitude of the T waves has further increased, while significant changes of QRS are absent. Tracings E through H, taken daily, show in Leads CR₃ through CR₅ a gradual return of the S-T segment to the base line accompanied by a decrease in the amplitude of T. In the last two tracings (I and J) significant changes of QRS and inversion of T are noted in the leads from the left side of the chest and in Lead I, indicating lateral wall infarction.

Summary.—There were two attacks of prolonged chest distress which occurred at an interval of two days. After the first attack the electrocardiogram was diagnostic of posterior infarction. In the earliest stage, one and one-half hours after the onset of symptoms, high T waves were seen in Leads II and III, associated with marked elevation of S-T. Later, in the healing stage of the posterior infarction, high T waves appeared in the chest leads. The second attack was followed by changes in the electrocardiogram which pointed to lateral infarction. The earliest stage was marked by further increase in the amplitude of the high T waves which had developed in the chest leads during the healing stage of the posterior infarction; there was also marked elevation of S-T. Six days passed before significant changes of QRS developed in the chest leads. During this period the high T waves gradually decreased in amplitude and became finally inverted.

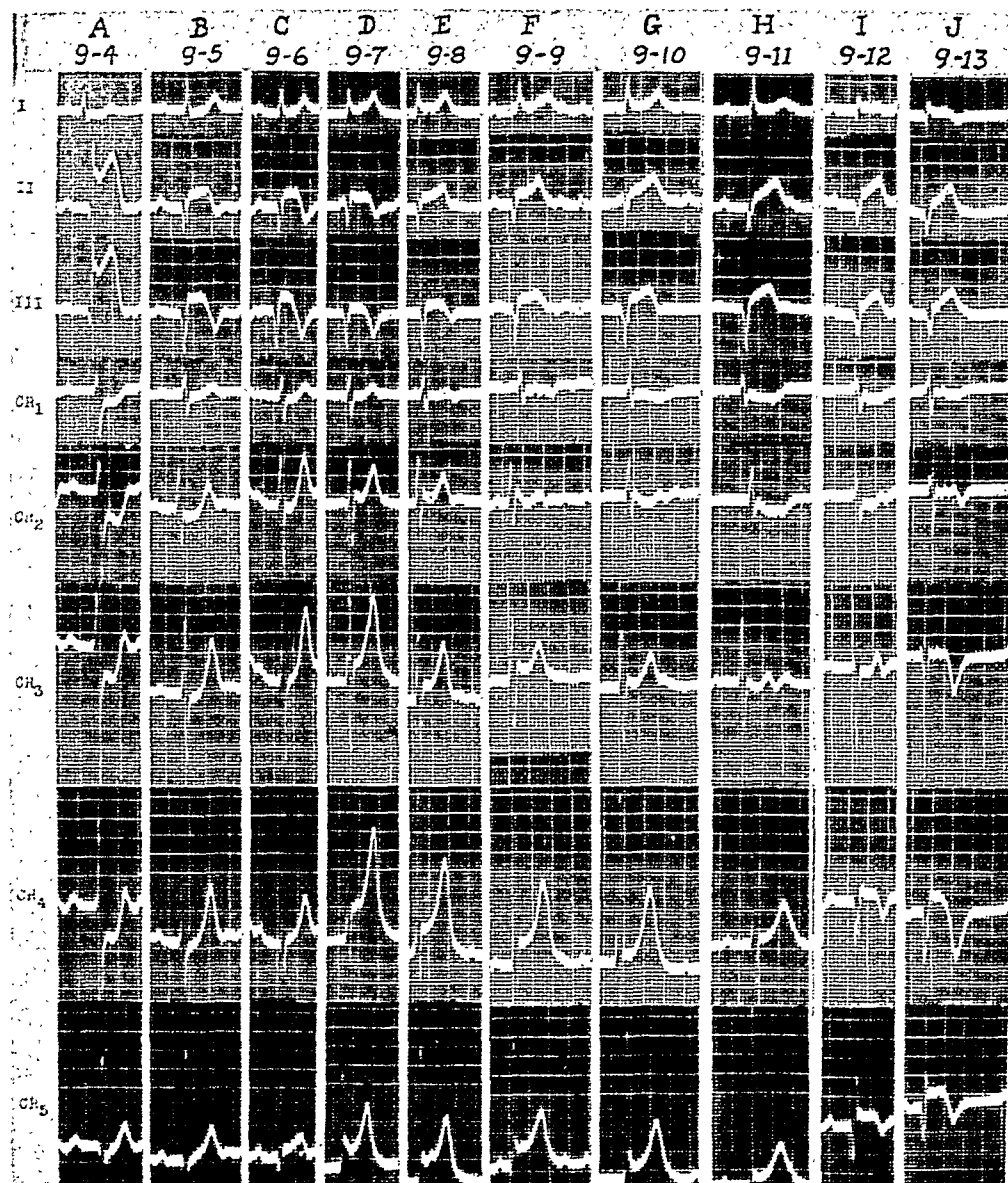


Fig. 7.—Case 23. Prolonged attacks of severe precordial distress occurred on September 4 and 6. After the first attack, signs of posterior wall infarction developed (tracings A and B). Tracing A, obtained one and one-half hours after the beginning of the first attack, shows in Leads II and III marked elevation of S-T and unusually high T waves. Significant changes of QRS in Leads II and III did not appear until a day after the attack (tracing B) and were simultaneous with inversion of T₂ and T₃ and with increase of the amplitude of T in the chest leads. Tracing D was obtained after the second attack of prolonged chest distress. It shows further increase of the T waves and elevation of S-T in Leads I and CR₁ through CR₅. Significant changes of QRS in these leads developed only six days after the attack (tracings I and J), when the T waves had become inverted. These changes pointed to lateral wall infarction.

COMMENT

The presence of myocardial infarction in the cases presented in this report (Table I) was proved by post-mortem examination in four instances, and in the remainder, by clinical, electrocardiographic, and other laboratory evidence. Anterior wall infarction was observed sixteen times and infarction of the pos-

terior wall, eleven times. In three cases, anterior and posterior infarctions occurred either simultaneously or in short sequence.

In all but two instances of infarction high T waves were observed during the earliest stage of infarction. They were seen in those leads in which inversion of T developed during the healing stage. In one of the cases where high T waves were absent (Case 6), the first electrocardiogram, taken on the day of the attack, already showed signs of healing (anterior) infarction, that is, inversion of T₁ and high T waves in Lead III.

The term "high T wave," as used in this report, needs amplification. In eight cases the amplitude of the significant T waves exceeded the maximum normal range; in six instances of posterior wall infarction the amplitude of T₃ was more than 3.4 mm.,¹⁵ in two cases of anterior wall infarction the T waves in the chest leads were of unusual amplitude.¹⁶ In no instance of anterior wall infarction were T waves in Lead I observed which had an amplitude above the maximum normal.

In thirteen instances the amplitude of the significant T waves was conspicuously in excess of the normal mean values which have been reported by various investigators.^{13,17}

In four of our cases electrocardiograms which had been obtained prior to the attack were available for comparison. Tracings taken shortly after the attack showed marked increase in the height of those T waves which later underwent inversion.

In thirteen instances where serial tracings were available (taken after the attack at intervals of several hours, or daily) it was possible to determine how long the high T waves persisted. In eight cases they were no longer present one day after the attack. In one of these cases (Case 21) high T waves still could be observed eight hours after the onset of symptoms but had disappeared five hours later. In Case 8 the high T waves, which were observed shortly after the beginning of the attack, were no longer present seven hours after the onset of symptoms.

Persistence of the high T waves for more than twenty-four hours was observed in five cases. In one case (Case 14) they were present for two weeks until death. Early death, that is, within several days after the attack, occurred in 60 per cent of the patients with persistent high T waves, but in only 14 per cent of the cases in which the high T waves disappeared within twenty-four hours. Persistent high T waves, as a rule, were associated with persistent elevation of the S-T junction.

High T waves in cases of myocardial infarction are possibly due to the release of potassium from the interior of injured muscle cells.¹³ They are part of the injury pattern²² like upward displacement of the S-T junction. In the cases of our study, high T waves were usually associated with abnormal elevation of S-T. However, in three cases of posterior wall infarction which showed high T waves in Lead III, and in three cases of anterior wall infarction in which high T waves were observed in the chest leads, abnormal elevation of S-T was absent. In five of these cases the S-T junction was either at the isoelectric level or was elevated within normal range. A sixth case (Case 4) which presented the

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM					FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q		CLINICAL AND ELECTROCAR- DIOGRAPHIC	AUTOPSY	
1	J. B.	58	3½ hours	In Lead I; huge T in CF ₄	Elevated 2.2 mm. in CF ₄	Normal	---	Three days later, R deflection absent in CF ₂ , its amplitude greatly diminished in CF ₄ . T ₁ much lower; inversion of T in CF ₂ and CF ₄	Anteroseptal infarction		The case shows the transition from the stage of subendo- cardial injury to in- farction involving the subepicardial muscle layers
2	H. L.	50	3 hours	In Leads I, CF ₂ , and CF ₄	No abnormal ele- vation	Absent in CF ₂	In CF ₄	After 13 hours, amplitude of T much diminished in Leads I, CF ₂ , and CF ₄ . T semi-in- verted in CF ₂ . After 5 days, T inverted in CF ₂ and CF ₄ , flat in Lead I	Anteroseptal infarction		
3	C. W.	51	Day of attack	In Leads CF ₂ , CF ₄ , and CF ₅	Abnormally ele- vated in Leads CF ₂ , CF ₄ , and CF ₅	Within normal limits	In CF ₂	One day later, the R wave has disappeared in CF ₂ and CF ₄ ; T lower in Lead I, lower and diphasic in CF ₂ , CF ₄ , and CF ₅	Anteroseptal infarction		
4	L. C.	36	3 hours	In Leads I, CR ₁ - CR ₆	Abnormally de- pressed in Leads I, CR ₂ -CR ₆	Within normal limits	---	18 hours after onset of symp- toms, abnormal Q in Lead I; R tiny in CR ₂ -CR ₃ , absent in CR ₄ . S-T elevated in leads where it was previously de- pressed. T of diminished volt- age in Leads I, CR ₂ -CR ₆ , diphasic in Leads I, CR ₂ -CR ₄ . After 3 days, inversion of T in Leads I, CR ₂ -CR ₆	Anteroseptal infarction		

5	H. B.	36	3 hours	In Leads I, CR ₂ -CR ₅	Abnormally elevated in CR ₂ -CR ₄	Within normal limits	—	10 weeks later, R absent in CR ₂ , of diminished voltage in CR ₂ -CR ₅ ; S-T not abnormally elevated; T of diminished voltage where it was previously high. Diphasic T in CR ₃	Anteroseptal infarction	Infarction scar in anterior wall of left ventricle close to interventricular septum	First electrocardiogram already showed changes usually observed in healing stage of anterior infarction
6	B. L.	56	Day of attack	In Lead III	Elevated 3 mm. in CF ₃ , depressed in Leads I and CF ₄	Rudimentary in CF ₂	—	3 weeks later, R of diminished amplitude in CF ₃ and CF ₄ ; no significant deviation of S-T; T sharply inverted in Leads I, CF ₂ , CF ₃ , and CF ₄ , abnormally high in Lead III. Death 2½ years after the attack	Anteroseptal infarction		
7	C. C.	55	2 hours	Increase in amplitude of T in CR ₂ , CR ₃ , and CR ₄	Abnormally elevated in CR ₂ and CR ₃	Of diminished amplitude in CR ₂ and CR ₃	—	1 day later, deep Q in CR ₂ ; R of diminished voltage in CR ₃ . The voltage of T diminished in CR ₂ , CR ₃ , and CR ₄ . 4 days later, R rudimentary in CR ₂ , absent in CR ₃ . 10 days later, T ₁ flat, inversion of T in CR ₂ , CR ₃ , and CR ₄	Anteroseptal infarction		An electrocardiogram taken 2 days prior to the attack was available for comparison.
8	H. W.	52	3½ hours	In CF ₁ , CF ₃ , and CF ₄	Abnormally elevated in Leads I, CF ₁ , CF ₃ , and CF ₄	Within normal limits	Small Q in CF ₃	7 hours after onset of symptoms, R absent in CF ₃ ; amplitude of T diminished in CF ₁ , CF ₃ , and CF ₄ ; beginning inversion of T in all chest leads. 12 hours after onset of symptoms, R rudimentary in CF ₄ , T inverted in Lead I and all chest leads	Anteroseptal infarction		
9	E. D.	45	1¼ hours	In Leads I, and CR ₂ -CR ₆	Abnormally elevated in Leads I and CR ₂ -CR ₅	Rudimentary in CR ₂ , absent in CR ₃ and CR ₄	In Leads I and CR ₂	1 day later, the T wave in Leads I, CR ₃ , and CR ₆ shows diminished voltage and is diphasic. The elevated S-T segments and high T waves in Leads CR ₁ -CR ₄ show almost no regressive changes until death 6 days after the attack	Extensive anterior infarction		

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)—CONT'D

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM						FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q	CLINICAL AND ELECTROCAR- DIOGRAPHIC		AUTOPSY		
10	P. T.	39	Day of attack	In Leads I, CF ₂ , and CF ₄	Abnormally ele- vated in CF ₂ and CF ₄	Within normal limits	—	Very slow decrease in voltage of T in Leads I, CF ₂ , and CF ₄ . Semi-inversion of T in these leads is noted only 11 days after the attack. No signifi- cant changes of QRS de- veloped	Anteroseptal infarction			
11	C. G.	63	5 hours	In CF ₂ and CF ₄	Abnormally ele- vated in CF ₂ and CF ₄	Absent in CF ₂ and CF ₄	—	1 day after the attack, T waves in CF ₂ and CF ₄ show dimin- ished voltage and terminal in- version. Death 3 days after the attack	Anteroseptal infarction	Recent anteroseptal infarction		
12	N. T.	41	5¾ hours	In CF ₃ and CF ₄	Abnormally ele- vated in CF ₃ - CF ₅	Tiny in CF ₃ , ab- sent in CF ₄	—	3 days after the attack, right bundle branch block. Pro- gressive changes of QRS and T in Leads II and III. inver- sion of T in CF ₂ and CF ₃ . Death 9 days after the attack	Anterior in- farction	Acute antero- septal and posterior in- farctions	Extensive recent in- farction of inter- ventricular septum, involving its entire width and extend- ing posteriorly over apical region of left ventricle	
13	N. E.	44	7 hours	In CF ₂ and CF ₃	Abnormally ele- vated in CF ₂ and CF ₃	Normal in CF ₂ and CF ₃ , of low voltage in limb leads	In Leads II and III					

	E. P.	56	Day of attack	Increase of T in Leads II, CF ₃ , and CF ₄	Abnormal elevation in CF ₃ and CF ₄	Slight decrease in amplitude of R in CF ₃ and CF ₄ , as compared with a previous tracing	—	8 hours after first tracing on day of attack, R is invisible in CF ₃ and of reduced amplitude in CF ₄ . Amplitude of T is somewhat diminished in Leads III, CF ₃ , and CF ₄ . A significant Q is seen in Lead III. T ₂ and T ₃ are diphasic. 1 day after attack, T ₂ and T ₃ are inverted. In the following 12 days, the elevated S-T and high T in CF ₃ and CF ₄ show almost no tendency to regressive changes. Death occurred 19 days after the attack	Acute antero-septal and posterior infarctions	Recent infarction of the whole width of the interventricular septum and of the anterior and posterior aspects of left ventricle	An electrocardiogram taken 11 months prior to the last attack was available for comparison
14											
15	M. N.	42	Day of attack	In Leads II and III	No abnormal elevation	Tiny in Lead III	—	3 days after onset of symptoms, significant Q in Leads II and III; T ₃ inverted, amplitude of T ₂ greatly reduced. Increase in height of T in CF ₂ and CF ₄	Posterior infarction		
16	J. M.	70	2½ hours	In Leads II and III	No abnormal elevation. Abnormal depression in all chest leads	Small in Lead III	—	3 days after onset of symptoms, significant Q and inverted T in Leads II and III. In the chest leads, depression of S-T very slight and T upright again	Posterior infarction		
17	J. T.	47	2½ hours	In Leads II and III	No abnormal elevation. Slight depression in CR ₂ -CR ₅	Low voltage in limb leads	—	7 hours after onset of symptoms, small Q in Lead II, deep Q in Lead III. Amplitude of T greatly diminished in Leads II, III, CR ₄ , and CR ₅ , increased in CR ₂ and CR ₃ . 19 hours after onset of symptoms, Q ₃ larger, T ₃ inverted. 29 hours after onset of symptoms, T ₂ inverted. 2 days after onset of symptoms, T in CR ₅ low and diphasic	Posterolateral infarction		
18	J. N.	50	3 hours	In Leads II and III	Abnormally elevated in Leads II and III	Within normal limits	In Leads II and III	8 days after attack, inversion of T ₂ and T ₃ . Death 10 days after attack	Posterior infarction		

TABLE I. CHANGES IN EARLY AND FOLLOW-UP ELECTROCARDIOGRAMS IN TWENTY-SEVEN INSTANCES OF MYOCARDIAL INFARCTION (TWENTY-FOUR CASES)—CONT'D

CASE	NAME	AGE	FIRST ELECTROCARDIOGRAM						FOLLOW-UP ELECTROCARDIOGRAM	DIAGNOSIS		REMARKS
			AFTER ONSET OF SYMPTOMS	HIGH T WAVES	S-T SEGMENT	R WAVES	SIGNIFICANT Q	CLINICAL AND ELECTROCAR- DIOGRAPHIC		AUTOPSY		
19	N. A.	69	2 hours	In CF ₃	Abnormally ele- vated in CF ₃ and CF ₅	Absent in CF ₃	In Leads I, CF ₃ , and CF ₅	Death one day after attack	Anterior in- farction			
20	A. P.	62	7 hours	In Leads II and III	Abnormally ele- vated in Leads II and III, de- pressed in Leads I, CR ₂ , and CR ₄	Within normal limits	Small Q in Leads II and III	15 hours after onset of symp- toms, significant Q in Leads II and III; S-T segment ap- proaching base line and T in- verted in Leads II and III. Very slight depression of S-T in CR ₂ and CR ₄	Posterior infarction			
21	W. D.	61	3 hours	In Leads II and III	Abnormally ele- vated in Leads II and III, de- pressed in Lead IV F	Within normal limits	Small Q in Leads II and III	8 hours after onset of symptoms, amplitude of T ₃ much reduced; diminished elevation of S-T in Lead III. 13 hours after onset of symptoms: in Lead III the Q wave broader but not yet of significant size; T ₃ low and M- shaped. 24 hours after onset of symptoms, no significant change. 32 hours after onset of symptoms, significant Q ₃ ; T ₂ diphasic, T ₃ inverted	Posterior in- farction			First appearance of significant Q ₃ 32 hours after onset of symptoms
22	H. W.	41	Day of attack ("right after onset")	In Leads II and III	Abnormally ele- vated in Leads II and III, de- pressed in Lead I	Within normal limits	In Leads II and III (were pres- ent prior to at- tack, as resid- ual of former attack)	6 days after attack, "Coronary T waves" in Leads II and III. 8 days after attack, T waves upright again in Leads II and III	Posterior in- farction			An electrocardiogram taken 1 day prior to attack was avail- able for compari- son

23	F. N.	59	1½ hours after first attack	In Leads II and III	Markedly elevated in Leads II and III; depressed in Leads I and CR ₃	Within normal limits	Small Q waves in Leads II and III	1 day after attack, significant Q waves and inverted T waves in Leads II and III. Increase in amplitude of T in CR ₂ -CR ₃	Posterior infarction	Two attacks occurred at an interval of 2 days. An electrocardiogram taken a day prior to the second attack was available for comparison. Although it already showed high T waves in Leads I, CR ₂ , and CR ₃ because of posterior infarction, an increase in the amplitude of these high T waves was observed after the second attack
			Within 24 hours of a new severe attack which occurred 2 days after first attack	In Leads I and CR ₃ -CR ₅	Markedly elevated in CR ₃ -CR ₅	Within normal limits	In Leads II and III (residuals of previous attack)	2 days after attack, amplitude of T reduced in CR ₃ -CR ₅ . Still marked elevation of S-T in CR ₃ -CR ₅ . 3 days after the attack, T smaller in Leads I, CR ₂ -CR ₃ . 5 days after attack, T of diminished voltage in Leads I, CR ₃ -CR ₅ . 6 days after attack, amplitude of R markedly reduced in Leads I, CR ₂ , CR ₃ , and CR ₅ ; QS deflection in CR ₄ ; significant Q in Leads I and CR ₅ ; T di-phasic in Leads I and CR ₃ , inverted in CR ₄ and CR ₅ . 7 days after attack, T sharply inverted in Leads I, CR ₂ -CR ₅	Anterolateral infarction	It took 6 days after the second attack until significant changes of QRS developed
24	J. S.	70	Day of attack	In Lead III (with terminal inversion)	Abnormally elevated in Lead III, depressed in CF ₃ and CF ₅	Of low amplitude in Lead III	In Lead II	9 days after attack, Q in Lead II, and downward deflection of QRS in Lead III have deepened. Elevation of S-T in Lead III has disappeared, T ₂ and T ₃ are inverted	Posterior infarction	Right bundle branch block

features of anterior wall infarction was unique, in our experience, inasmuch as it showed high T waves, especially in the chest leads, coupled with abnormal depression of S-T. Downward displacement of S-T in limb and chest leads is sometimes observed in patients in whom repeated anginal attacks constitute a prolonged "prodromal stage" prior to the appearance of classical signs of myocardial infarction. In such patients, depression of S-T is thought to indicate marked coronary insufficiency which has caused injury primarily to the subendocardial muscle layers.¹⁸⁻²¹ We believe that the first tracing in Case 4 depicts a transitional stage which was the result of an extension of injury from the subendocardial to the subepicardial muscle layers, possibly due to progression from incomplete to complete coronary occlusion.

In fifteen cases high T waves appeared earlier than significant changes in the QRS complexes. The latter were either absent altogether in the early stage or (in five cases) there were some suspicious changes of QRS, such as a decrease in the size of the R deflections or small Q waves in Leads II and III. In most of these cases significant changes of QRS developed within twenty-four hours after the onset of symptoms when the high T waves were already in the regressive stage. In one case (Case 23) significant Q waves did not appear until six days after the attack. There were two instances in which significant changes of QRS failed to develop while the high T wave became gradually inverted.

In five cases high T waves in the earliest stage of myocardial infarction were associated neither with abnormal elevation of S-T nor with significant changes of QRS. These cases included three instances of posterior wall infarction (Cases 15, 16, and 17) and two instances of anterior infarction (Cases 1 and 4). Thus, in 18 per cent of our cases, high T waves represented the leading diagnostic sign in the earliest stage of myocardial infarction.

SUMMARY

Twenty-seven instances of myocardial infarction were studied, in which the first electrocardiogram was taken as early as one and one-quarter hours, and not later than twelve hours, after the onset of symptoms. Follow-up tracings were obtained in all but two of these cases. In thirteen cases serial records, taken daily or at intervals of several hours, were available for study.

In twenty-five cases the earliest electrocardiographic signs of infarction were high T waves, the majority of which became inverted in the healing stage of infarction. In most of the cases the high T waves were no longer present twenty-four hours after the attack. In five instances where the T waves persisted for several days, early mortality was as high as 60 per cent, as compared with 14 per cent in the cases where the high T waves underwent regression within twenty-four hours.

The high T waves are thought to be part of the injury pattern. They were accompanied by abnormal elevations of S-T in twenty-one cases. In five instances elevation of S-T was either absent or within normal range. In one instance huge upright T waves were associated with marked depression of S-T.

In the majority of the cases high T waves preceded the development of significant changes in the QRS complex. The latter usually appeared within twenty-four hours after the onset of symptoms, when the high T waves were already in the regressive stage. In one instance characteristic changes in QRS did not appear until six days after the attack, and in two instances they failed to develop at all.

In five cases high T waves were not associated with abnormal elevation of S-T, nor with significant changes in QRS. Thus, they represented the leading diagnostic sign in the early stage of myocardial infarction.

REFERENCES

1. Wood, F. C., and Wolferth, C. C.: Huge T Waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9:706, 1934.
2. Cooksey, W. B.: Discussion of a Paper by A. R. Barnes Before the Central Society for Clinical Research, *J. A. M. A.* 101:2148, 1933.
3. Bohning, A., and Katz, L. N.: Unusual Changes in the Electrocardiograms of Patients With Recent Coronary Occlusion, *Am. J. M. Sc.* 186:39, 1933.
4. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *Arch. Int. Med.* 5:142, 1929.
5. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22:8, 1918.
6. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26:244, 1920.
7. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14:195, 1928.
8. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries; in Levy, R. L. (editor): *Diseases of the Coronary Arteries and Cardiac Pain*, New York, 1936, The Macmillan Company.
9. Johnston, F. D., Hill, J. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 889, 1935.
10. Rothschild, M. A., Mann, H., and Oppenheimer, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, *Proc. Soc. Exper. Biol. & Med.* 23:253, 1926.
11. White, P. D.: *Heart Disease*, New York, 1944, The Macmillan Company.
12. Levine, S. A.: *Clinical Heart Disease*, Philadelphia and London, 1945, W. B. Saunders.
13. Ashman, R., and Hull, E.: *Essentials of Electrocardiography*, New York, 1941, The Macmillan Company.
14. Katz, L. N.: *Electrocardiography*, Philadelphia, 1941, Lea and Febiger.
15. Stewart, C. B., and Manning, G. W.: A Detailed Analysis of the Electrocardiograms of 500 R. C. A. F. Aircrew, *AM. HEART J.* 27:502, 1944.
16. Deeds, D., and Barnes, A. R.: The Characteristics of the Chest Lead Electrocardiograms of 100 Normal Adults, *AM. HEART J.* 20:261, 1940.
17. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1000 Healthy Aviators, *AM. HEART J.* 27:524, 1944.
18. Buechner, F.: Deutung des Elektrokardiogramms bei den Durchblutungsstoerungen des Herzmuskels, *Klin. Wchnschr.* 17:1713, 1938.
19. Master, A. M., Gubner, R., Dack, S., and Jaffee, H. L.: Differentiation of Acute Coronary Insufficient With Myocardial Infarction From Coronary Occlusion, *Arch. Int. Med.* 67:647, 1941.
20. Bailey, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, *AM. HEART J.* 31:677, 1946.
21. Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationship to Positive Displacement; An Experimental Study, *AM. HEART J.* 29:220, 1945.
22. Bailey, R. H., La Due, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, *AM. HEART J.* 27:164, 1944.

ELECTROLYTE CHANGES AND THE ELECTROCARDIOGRAM IN DIABETIC ACIDOSIS

HELEN EASTMAN MARTIN, M.D., AND MAXINE WERTMAN, A.B.
LOS ANGELES, CALIF.

THE changes in the electrocardiogram in diabetic acidosis are well known since the report and review of Bellet and Dyer,¹ and consist of depression of the S-T segment, lengthening of the Q-T interval, and alterations in the amplitude and direction of the T waves. The fact that these changes are reversible and the electrocardiogram reverts to normal after several days has strongly suggested that alterations in electrolyte balance are important factors in the production of the abnormalities.

METHOD AND MATERIAL

The study to be reported was undertaken to see if there was any correlation between pH, calcium, potassium, and magnesium levels and the electrocardiographic changes. No previous similar complete electrolyte study has been reported to our knowledge. Thirteen patients who entered the hospital in severe diabetic acidosis (carbon dioxide combining power under 9 milliequivalents, calculated as bicarbonate) were followed for several days with synchronous determinations of blood chemistry and electrocardiograms. The chemical determinations in all patients included serum calcium, potassium, sodium, and magnesium levels, total plasma protein, blood sugar, and carbon dioxide combining power. In order to calculate the ionized calcium fraction, additional studies in five patients included the determination of the albumin and globulin fraction and blood pH. A detailed report of the results and methods, including the formula used for calculation of the ionized calcium value, has been described elsewhere.² The Q-T interval for each electrocardiogram was calculated by the formula of Ashman³ with the corrections suggested for age and sex.

RESULTS

The results of the electrolyte changes correlated with the electrocardiographic changes are summarized in Table I. The relationships of the various changes are analyzed separately in Tables II to VI.

Table II summarizes the correlation between the depression of the S-T segment and acidosis. When present, the depression of the S-T segment, with a

From the Department of Medicine of the University of Southern California School of Medicine and the Los Angeles County Hospital.

Received for publication April 10, 1947.

straight upsweep into the T wave, occurred usually during the first twenty-four hours. It was felt, therefore, that this factor might be related to acidosis. In nineteen instances of depressed S-T segment, the carbon dioxide combining power or pH was low in sixteen, or 84 per cent. Of the twenty-nine instances of isoelectric S-T segments, twenty, or 69 per cent, were associated with normal pH and carbon dioxide combining power, while nine, or 31 per cent, occurred with low pH or low carbon dioxide combining power. The depressed S-T segments which occurred when there was acidosis returned to the isoelectric line at the same time that the acidosis was corrected (Cases 2, 4 to 6, 8, 9, 12, and 13, and Table I).[✓] It is to be noted that in our series of diabetic patients there was no definite correlation between the level of the serum potassium and depression of the S-T segment. (This is contrary to the experimental work in dogs,⁴ where depression of the S-T segment occurred with moderate elevation of the serum potassium levels.) Further studies will be necessary to establish the mechanism of this change in the S-T segments.

Table III summarizes the results of total serum calcium and potassium levels, as correlated with the Q-T interval, in eight patients. Twenty-two records showed prolonged Q-T intervals, and of this group only four had low calcium levels and one a low potassium concentration.

With the shifts in pH and total protein which occur during the therapy of diabetic acidosis, it was felt that the level of ionized calcium might not always follow the total calcium concentration, and that this factor might be important in the prolongation of the Q-T interval. Table IV gives the relationship between total and ionized serum calcium values in five patients. Of twenty-five total serum calcium concentrations only four were abnormal, while fifteen of the calculated ionized values were below normal. Also, the ionized calcium fraction represented a variable fraction of the total serum calcium concentration (39 to 52 per cent).

Table V shows the results of these detailed studies of total calcium, ionized calcium, and potassium in five patients. In eighteen determinations of the Q-T interval, five were markedly prolonged, twelve were slightly prolonged, and one was normal. In ten instances, these abnormalities were associated with decreased ionized calcium levels, and four, in addition, showed low potassium concentrations. In six instances, slightly prolonged Q-T intervals were associated with normal serum calcium, total and ionized fraction, and normal serum potassium levels.

Summarizing Tables III and V, there were thirty-seven records with prolonged Q-T intervals. In sixteen, or 43 per cent, of these the total or ionized calcium and potassium (one or all) were below normal; while in twenty-one, or 57 per cent, of the records with prolonged Q-T interval, the total and ionized calcium and potassium were within the normal range at the time the record was made. It is to be noted, however, that of the seven records with markedly prolonged Q-T intervals, in six abnormalities of calcium or potassium levels, or both, were present when the records were made. These facts suggest that in over 50 per cent of the instances of prolonged Q-T interval there was some

TABLE I. GENERAL SUMMARY OF RESULTS

DAY	HOUR	pH	MEQ. HCO_3^-	MEQ. Ca	MEQ. Ca^{++}	MEQ. Mg	MEQ. K	CYCLE LENGTH	Q-T INTER-VAL	CALCULATED Q-T INTERVAL	S-T SEGMENTS	T ₁	T ₂	T ₃	TCF ₁
<i>1. A. B., White Man, 69 Years of Age, No. 723-522</i>															
1	2	7.28	10.0	4.35	2.15	1.47	5.38	.60	.32	.31	Isoelectric	Isoelectric	▲ Low	▲ Very low	▲ Slightly low
1	20	7.60	24.0	4.30	2.20	1.06	1.90	.75	*	.35	Isoelectric	Isoelectric	▼ Diphasic; very low	▼ Very low	▲ Very low
2	1	7.65		4.40	2.20	1.39	2.77	.71	*	.34	Isoelectric	Isoelectric	▲ Very low	▲ Almost isoelectric	▲ Very low
2	20	7.63		4.30	2.15	1.47	2.18	.75	*	.35	Isoelectric	Isoelectric	▲ Very low	▲ Almost isoelectric	▲ Very low
3	7.59			4.25	2.15	1.39	3.36	.74	*	.35	Isoelectric	Isoelectric	▲ Almost isoelectric	▲ Almost isoelectric	▲ Very low
4	7.60			4.45	2.20	1.56	5.13	.91	.43	.38	Isoelectric	▲ Very low	▲ Normal	▲ Low	▲ Normal
5	7.57			4.40	2.30	1.23	6.64	.81	.39	.36	Slight elevation of S-T ₂ and S-T ₃	▲ Very low	▲ Slightly low	▲ Slightly low	▲ Slightly low
6	7.52			4.75	2.30	1.31	4.31	.80	.40	.36	Isoelectric	▲ Very low	▲ Slightly low	▲ Slightly low	▲ Slightly low
7	7.55			4.50	2.25	1.39	6.13	.77	.40	.35	Isoelectric	Isoelectric	▲ Very low	▲ Very low	▲ Very low
<i>2. T. B., Colored Woman, 19 Years of Age, No. 683-113</i>															
1	0	7.05	7.5	5.25	2.15	1.98	6.72	.41	.28	.26	Depressed	▲ Rapid rise, low	▲ Rapid rise, low	▲ Low	▲ Low
1	6	7.29	9.5	4.65	2.05	1.16	5.42	.49	.34	.29	Very slight depression	▲ Slightly low	▲ Slightly low	▼ Low	▲ Normal
2	7.55	22.0		4.80	2.20	0.56	3.20	.82	.51	.37	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
3	7.55			4.70	2.25	1.40	4.56	.84	.43	.37	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
4	7.58			5.00	2.25	1.48	4.56	.90	.42	.38	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal

3. N. W., White Woman, 44 Years of Age, No. 319-307

1	20	7.58	17.0	3.85	1.60	0.82	3.41	.58	.38	.32	Isoelectric	A Low	A Normal	A Slightly low	A
---	----	------	------	------	------	------	------	-----	-----	-----	-------------	-------	----------	----------------	---

4. B. M., White Man, 19 Years of Age, No. 968-418

1	2	7.12	7.0	5.70	2.25	2.13	7.28	.43	.28	.26	Isoelectric I, sagging II and III, slight elevation IV	A Normal	A Rapid rise, slightly low	A Rapid rise, very low	A Very high (12 mm.)
1	9	7.51	18.5	4.65	2.05	1.56	5.00	.48	.29	.28	Isoelectric	A Low	Diphasic—low		A Normal
2		7.58		4.40	2.05	1.23	5.74	.63	.36	.32	Isoelectric I and III, slight elevation II and IV	A Normal	Low		A Normal
5		7.51	26.0	4.85	2.10	1.47	5.64	.71	.31	.33	Slight elevation II, III, IV	A Normal	Low	Low	A Normal

5. E. S., White Woman, 19 Years of Age, No. 962-393

1	10	7.32	4.9	5.20	2.45	1.56	4.26	.41	*	.24	Depressed	A Rapid rise, ? low	A Rapid rise, low		
1	13	7.49	16.5	5.00	2.40	1.31	2.20	.44	*	.27	Depressed	A Rapid rise, very low	A Rapid rise, very low	? Low	Low
1	16	7.64	23.0	5.15	2.30	1.39	2.18	.43	*	.27	Depressed	A Rapid rise, very low	A Rapid rise, very low		Low
2		7.51	17.5	4.90	2.30	1.88	3.85	.59	.46	.32	Very slightly depressed	A Very low, broad	A Very low, broad	Low	Low
4		7.32		3.55	1.85	1.15	3.49	.52	.32	.30	Isoelectric	A Very low	A Normal	Normal	Normal
37		7.33		4.95	2.05	1.39	6.18	.59	.35	.32	Slight elevation S-T ₂ and S-T ₃	A Normal	High	Normal	Normal

6. R. B., White Man, 40 Years of Age, No. 950-958

1	2		<4.5	5.55		2.95	5.11	.52	.37	.29	Sagging	A Rapid rise, normal	A Normal		A Normal
6				4.45		1.39	4.98	.72	.37	.34	Isoelectric	A Normal	A Normal		A Normal
13				4.65		1.23	5.54	.73	.36	.34	Isoelectric	A Normal	A Normal		A Normal

TABLE I. GENERAL SUMMARY OF RESULTS—(CONT'D)

DAY	HOUR	pH	MEQ. HCO_3	MEQ. Ca	MEQ. Ca^{++}	MEQ. Mg	MEQ. K	CYCLE LENGTH	Q-T INTER-VAL	CALCULATED Q-T INTERVAL	S-T SEGMENTS	T ₁	T ₂	T ₃	TCF ₄
7. F. C., White Boy, 12 Years of Age, No. 211-641															
1	3		9.0	5.25		2.46		.43	.27	.26	Isoelectric	▲ Rapid rise, low	▲ Rapid rise, low	Isoelectric	▲ Normal
4			8.0	4.45		1.56	4.87	.63	.34	.32	Isoelectric	▲ Low, broad	▼ Low	▼	▼
10				3.95		1.06	4.26	.73	.38	.34	Isoelectric	Isoelectric	▼	▼	▼
21				4.80		1.35	7.20	.56	.29	.30	Isoelectric	▲ Normal	▲ Normal	▼	▲ Low
33				5.50		1.39	5.87	.61	.32	.30	Isoelectric	▲ Normal	▲ Normal	▼	▲ Low
8. E. R., White Man, 40 Years of Age, No. 949-632															
1	20		19.5	4.30		0.98	3.82	.48	.34	.28	Sagging S-T ₁ and S-T ₂	▼ Low	▼ Low	Isoelectric	▼
8				4.40		1.48	5.08	.74	.40	.34	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal
9. J. S., White Woman, 18 Years of Age, No. 866-215															
1	0		5.5	5.50		2.46		.50	.35	.29	Sagging	▲ Rapid rise, low	▲ Rapid rise, low	▲ Rapid rise, low	▼ ?
1	20		21.5	3.85		1.52		.71	.37	.34	Isoelectric	▲ Low	▲ Low	Isoelectric	▲ Low
5				5.65		1.23		.63	.35	.33	Isoelectric	▲ Normal	▲ Normal	▼	▲ Normal

10. M. K., White Boy, 16 Years of Age, No. 947-988

1	2		5.5	5.25		2.21		.48	.34	.28	Isoelectric	▲ Normal	▼	▲
1	21		20.5	4.95		1.30		.50	.33	.28	Isoelectric	▲ Broad-low		▲
7				5.20		1.72	5.84	.81	.40	.35	Isoelectric	▲ Normal	▼	▲ Normal

11. J. W., White Boy, 13 Years of Age, No. 949-854

1	0		<4.5	5.15		1.56		.47	.32	.27	Isoelectric	▲	▼ ?	▲
1	19		14.0	5.45		1.23	3.52	.64	*	.32	Isoelectric	Broad, low	▼	▲
6				4.85		1.31	5.67	.62	.36	.31	Isoelectric	▲ Normal	Very low	▲ Normal

12. T. A., White Boy, 17 Years of Age, No. 34-034

1	4		6.5	4.15		1.83	5.57	.46	.32	.27	Sagging	▲ Slightly low	▼	▲
2				4.00		0.98	4.36	.65	.36	.32	Isoelectric, S-T ₁ and S-T ₂ , slight elevation III	▲ Slightly low	▼	▲
3				4.40		1.23	5.93	.57	.36	.30	Isoelectric	▲ Normal	Low	▲ Slightly low

13. A. D., White Woman, 39 Years of Age, No. 954-618

1	3		12.5	4.40		1.11	4.26	.60	.33	.32	Slight sagging S-T ₂ and S-T ₃	▲ Very low	▲ Low	▲ Low
2				4.55		1.31	7.21	.71	.40	.34	Isoelectric	▲ Normal	▲ Normal	▲ Low

If the carbon dioxide combining power is not given after the first 24 hours, this was because it had become normal, and was not checked further in most instances.
*Unable to calculate.

factor other than serum calcium and potassium responsible. It is possible that the normal range of Q-T interval may not be wide enough, even when corrected for age or sex. Some undetermined factor which persists for several days or weeks may also be present following severe diabetic acidosis. It is seen from Table I that in most instances, even after four or five days, most of the Q-T intervals are still slightly prolonged.

TABLE II. ACIDOSIS AND THE S-T SEGMENT CHANGES

pH DETERMINATIONS (FIVE PATIENTS)		
pH LEVEL	DEPRESSED S-T SEGMENT	ISOELECTRIC S-T SEGMENT
7.0-7.25	2	0
7.25-7.35	2	3
7.35-7.65	3*	15

CO ₂ COMBINING POWER (THIRTEEN PATIENTS)		
CO ₂ C. P.	DEPRESSED S-T SEGMENT	ISOELECTRIC S-T SEGMENT
0-10 meq.	8	4
10-20 meq.	4	2
20+ meq.	0	5

*These values were all in the same patient and did not check closely with the CO₂ combining power.

TABLE III. CORRELATION OF CALCIUM AND POTASSIUM CONCENTRATION WITH Q-T INTERVAL (EIGHT PATIENTS)

SERUM LEVELS CA AND K	Q-T INTERVAL		
	MARKEDLY PROLONGED	SLIGHTLY PROLONGED	NORMAL
Ca and K both normal	1	10	1
Ca low, K normal	1	2	
K low, Ca normal		1	
Only Ca determined:			
Normal		4	
Low		1	

One of the most striking changes in the electrocardiogram in diabetic acidosis is the occurrence of abnormal T waves, particularly very low or isoelectric waves. As seen in Table VI, in ten records with very low T waves nine were associated with very low serum potassium levels. Insulin is known to cause a definite decrease in serum potassium levels and urinary excretion.^{2,5,6-8} This was found to occur most strikingly in the first twenty-four hours of intensive insulin therapy and has been reported in detail elsewhere.² As the serum potassium concentra-

*These values were all in the same patient and did not check closely with the CO₂ combining power.

TABLE IV. CORRELATION OF IONIZED AND TOTAL CALCIUM CONCENTRATIONS (FIVE PATIENTS)

PATIENT	TOTAL Ca CONCENTRATION (MEQ.)	CALCULATED IONIZED Ca (MEQ.)	PER CENT OF TOTAL CALCIUM AS [Ca++]
A. B.	4.45	2.20	49
	4.40	2.30	52
	4.75	2.30	48
	4.50	2.25	50
T. B.	5.25	2.15	46
	4.65	2.05	44
	4.80	2.20	46
	4.70	2.25	48
	5.00	2.25	45
N. W.	3.85	1.60	42
B. M.	5.70	2.25	39
	5.10	2.00	39
	4.65	2.05	44
	4.40	2.05	47
	4.85	2.10	43
E. S.	5.20	2.45	47
	5.00	2.40	48
	5.15	2.30	45
	4.90	2.30	47
	3.55	1.85	52
	4.95	2.05	41

TABLE V. CORRELATION OF TOTAL AND IONIZED CALCIUM LEVELS AND POTASSIUM LEVELS WITH Q-T INTERVAL (FIVE PATIENTS)

	MARKEDLY PROLONGED	SLIGHTLY PROLONGED	NORMAL
Total and ionized Ca and K normal		6	
Total Ca and K normal; ionized Ca low	2	5	1
Total Ca normal; [Ca++] and K low	1		
Low total and ionized Ca; low K	1	1	
Total and ionized Ca normal; low K	1		

TABLE VI. CORRELATION OF T-WAVE CHANGES WITH SERUM POTASSIUM LEVELS

	NORMAL AMPLITUDE OF T WAVES	DECREASED AMPLITUDE OF T WAVES	VERY LOW TO ISOELECTRIC T WAVES	HIGH T WAVES
Normal serum K levels (4.2-5.8 meq.)	14	12	1	
Low serum K levels (under 4.2 meq.)	1	1	9	
High serum K levels (over 5.8 meq.)	3			1

tion returned to normal levels, the T waves increased in amplitude in most instances. Normal or moderately low T waves were associated with normal potassium values. High T waves occurred in a few patients and were associated with elevated potassium levels. No examples of intraventricular block were seen.

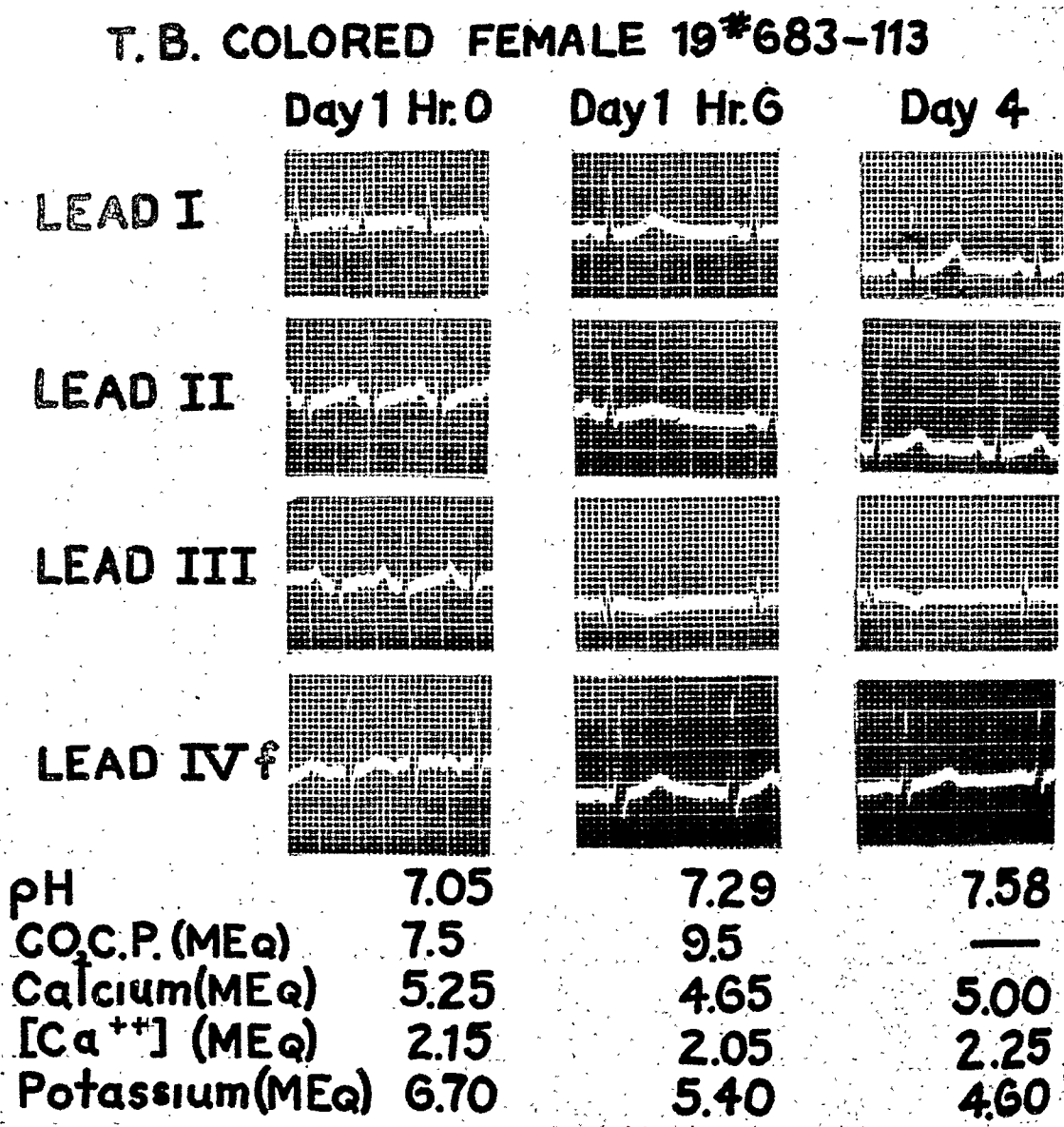


Fig. 1.—Case 2 of Table I. See text for discussion.

The relationship of the magnesium levels to the electrocardiographic changes must remain unsettled, as there have been no studies in the experimental animal on the effect of low magnesium levels on the electrocardiogram. Very low levels were reached in some of our patients, and even after four to seven days the values had not always returned to the normal level for the method used in this laboratory. While a few moderately elevated values of serum magnesium

were obtained, they were not associated with any specific electrocardiographic change. They were not in the range known to produce conduction changes.

Serum sodium levels, even with parenteral therapy, remained relatively constant. It was felt, therefore, that this ion did not enter into the problem of the electrocardiographic changes.

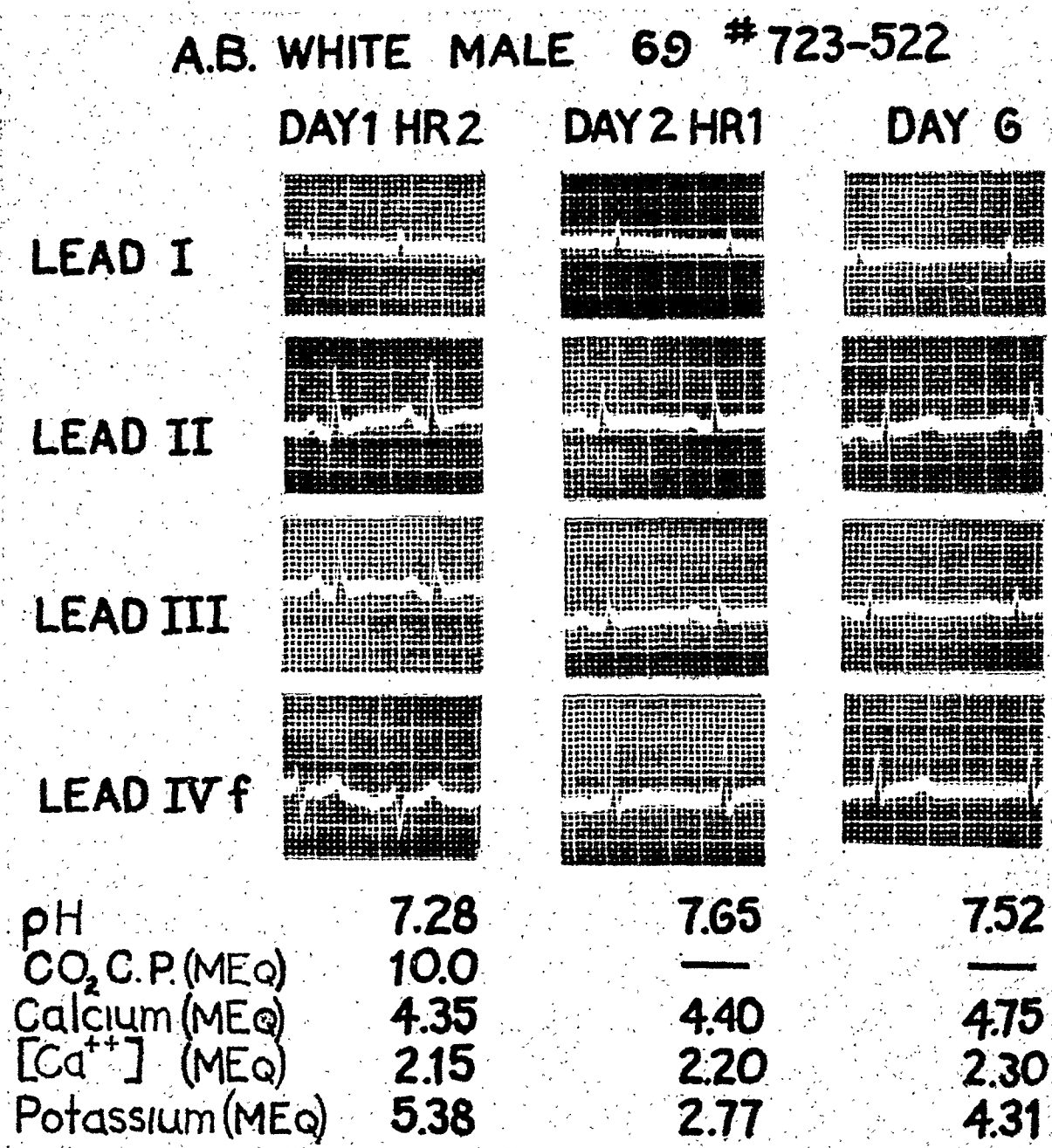


Fig. 2.—Case 1 of Table I. See text for discussion.

Relatively few and insignificant changes occurred in amplitude or character of the P wave or the QRS complex. In only one instance was there a shift in axis deviation during therapy.

The only precordial lead taken in these studies was CF₄. No changes were noted in this lead which were not shown by the indirect leads.

The findings discussed in the preceding material are illustrated in more detail by the electrocardiograms and electrolyte changes in four patients (Figs. 1-4). In Fig. 1, (Case 2, T. B., Table I) Tracing 1, taken on entry before any treatment, shows a striking sagging of the S-T segments with a straight rise into

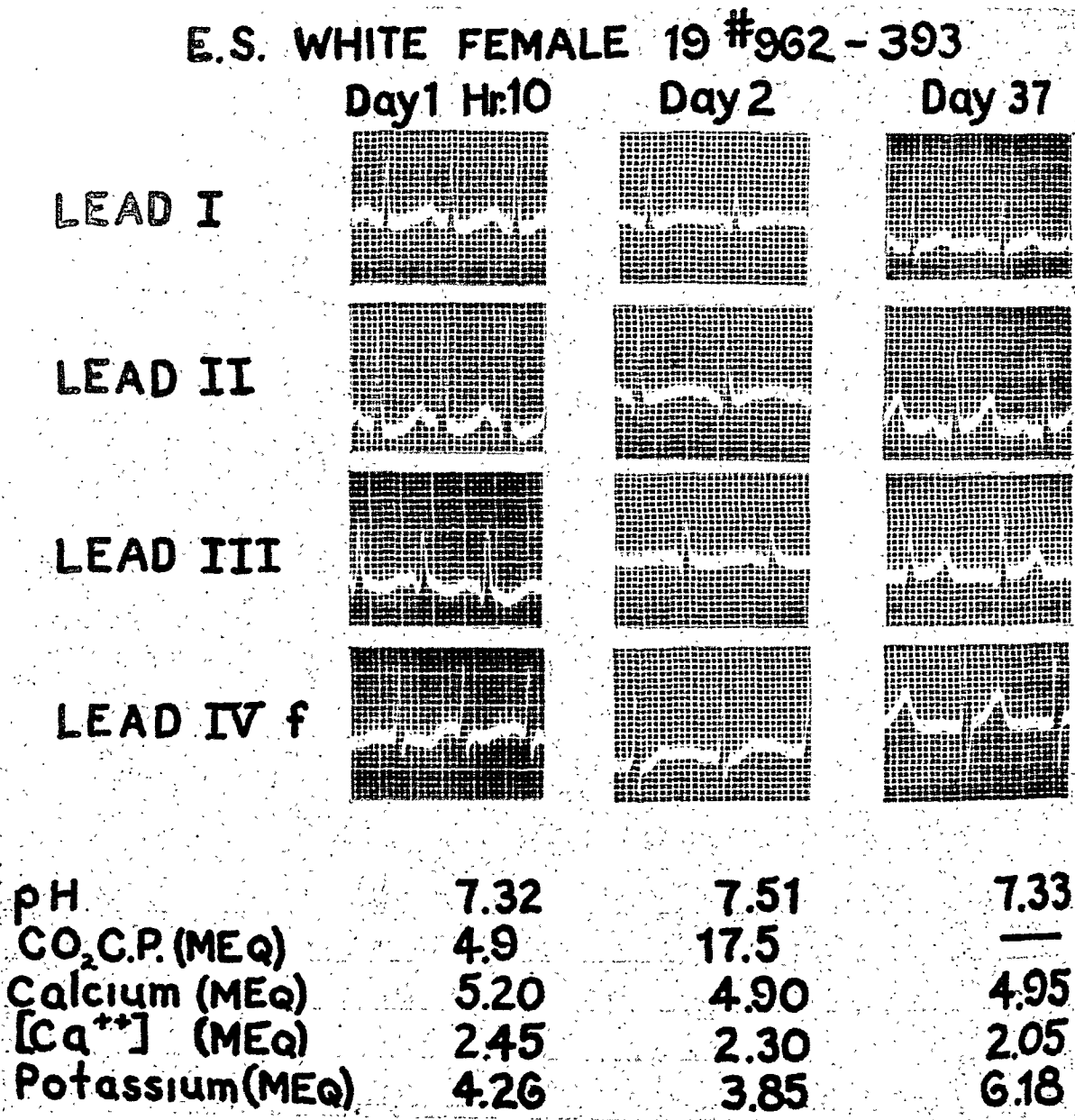


Fig. 3.—Case 5 of Table I. See text for discussion.

low amplitude T waves in the standard leads, plus a marked tachycardia. At this time the pH was 7.05 and serum potassium 6.70 milliequivalents. Six hours later (Fig. 1, Tracing 2), following intensive treatment, the pH had risen to 7.29 (carbon dioxide combining power still only 9.5 milliequivalents; serum potassium 5.40 milliequivalents) and the sagging of the S-T segments is seen to

have disappeared. At this time (six hours after entry) T_2 is broad and the Q-T interval is prolonged (0.34 second, with a calculated normal of 0.288 second), although the serum levels of total calcium and potassium were normal. The ionized calcium was definitely below normal, however (2.05 milliequivalents).

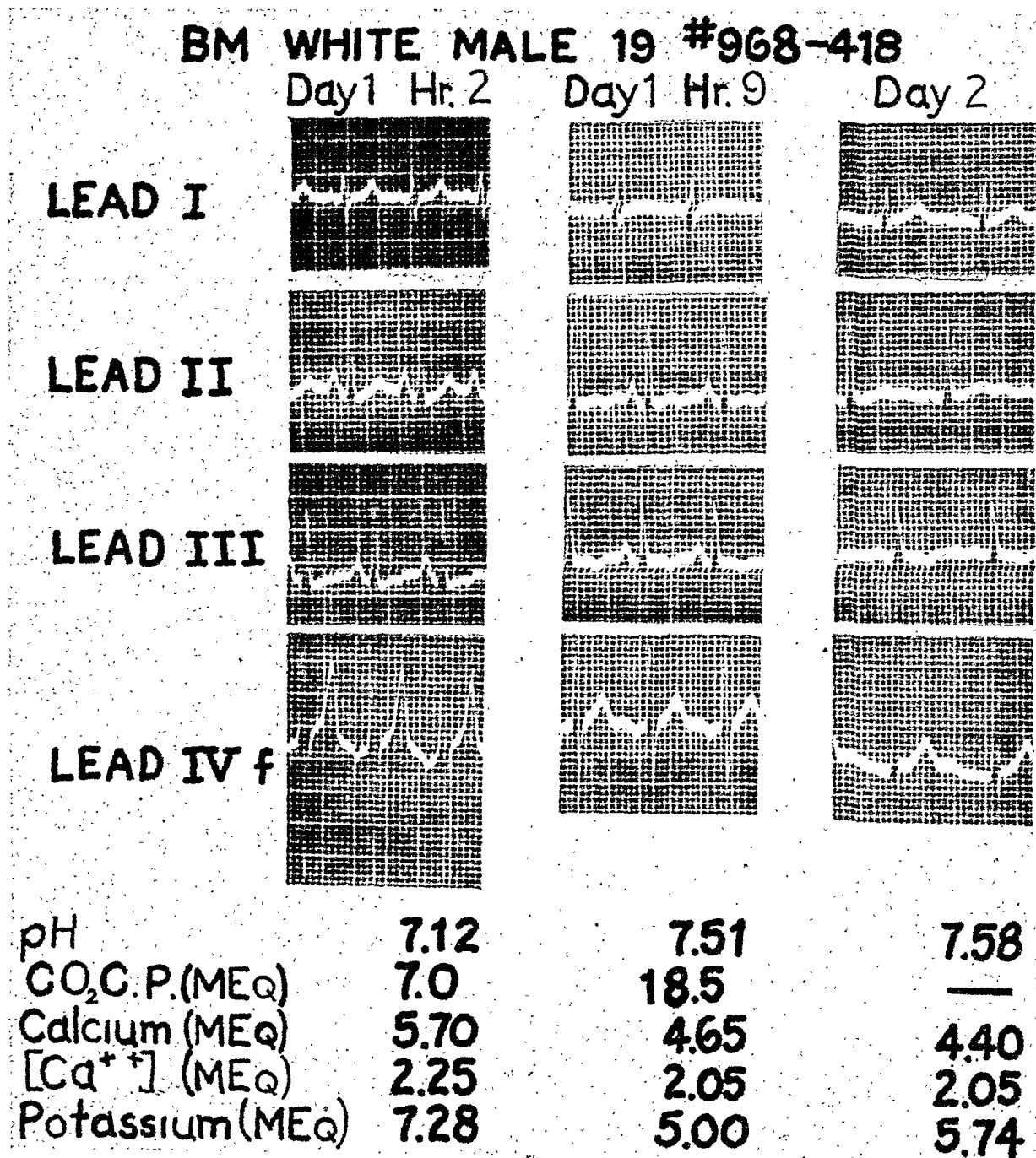


Fig. 4.—Case 4 of Table I. See text for discussion.

By the fourth day the electrocardiogram was entirely normal except for slight prolongation of the Q-T interval and the electrolytes were essentially normal except for slight decrease in serum magnesium.

In Fig. 2 (Case 1, A. B., Table I) the first tracing, taken two hours after entry, shows no sagging of the S-T segment. When this tracing was made there

was only moderate acidosis (pH 7.28) and the potassium concentration was in the normal range (5.38 milliequivalents). The Q-T interval is seen to be normal, as were total serum calcium and potassium concentrations. The ionized calcium was slightly reduced. The second tracing, taken twenty hours after entry, shows a marked reduction in the amplitude of the T waves, which was associated with a drop in the serum potassium from 5.38 to 2.77 milliequivalents. With return of the potassium to normal (4.31 milliequivalents), the T waves increase in amplitude (Day 6, Tracing 3). At this time the only abnormality in the electrocardiogram is a long Q-T interval (0.43 second, with a calculated normal of 0.38 second). All chemistry was normal except for slight reduction of the ionized calcium and magnesium levels.

Fig. 3 (E. S., Case 5, Table I) shows many striking changes. The first tracing, taken ten hours after entry, illustrates depression of the S-T segment with a rapid rise into low amplitude T waves in Leads I and II. At this time the pH was 7.32, and the serum potassium was normal (4.26 milliequivalents). On the second day (second tracing) the T waves are broad and flat and the potassium level had decreased (3.85 milliequivalents). The Q-T interval is definitely prolonged (0.46 second as contrasted to a calculated value of 0.32 second). The serum calcium values, total and ionized, were within the normal range. Tracing 3, taken on the thirty-seventh day, shows a marked increase in amplitude of the T waves, associated with an elevated serum potassium level (6.18 milliequivalents). The Q-T interval is still slightly prolonged (0.35 second as contrasted to a calculated normal of 0.32 second).

Fig. 4 (B. M., Case 4, Table I) shows very high T waves in the fourth lead of Tracing 1 taken two hours after entry, sagging of the S-T segments in Leads II and III, and a prominent S_1 . At this time, the serum potassium concentration was definitely elevated (7.28 milliequivalents). Tracing 2, taken nine hours after entry to the hospital, shows a decrease of the T wave in Lead CF_4 to normal amplitude, associated with a normal serum potassium level (5 milliequivalents). Tracing 3, taken two days after entry, is essentially normal with disappearance of S_1 ; the electrolytes were normal except for decreased ionized calcium and magnesium.

DISCUSSION

The problem of the pathogenesis of the electrocardiographic changes in diabetic acidosis is complex. There are several factors which may be responsible:

1. Changes in pH and extracellular electrolytes.
2. Changes in intracellular electrolytes due to (a) changes in extracellular electrolytes, (b) nutritional state of the muscle due to anoxia, lack of vitamins, and depletion of cardiac glycogen, and (c) effect of retention of waste products due to impaired renal function.
3. Alterations in the rate and depth of breathing associated with the Kussmaul type of respiration, shifts in diaphragm levels secondary to abdominal distention, and the character of the respiratory effort.

The fact that changes in pH and serum calcium and potassium do cause changes in the electrocardiogram is shown by our results in diabetic acidosis, and in a variety of experimental and clinical conditions.

The electrolyte and pH changes produced experimentally or occurring in certain diseases produce definite and specific electrocardiographic changes. In the alkalosis produced by hyperventilation⁹ or by the ingestion of sodium bicarbonate¹⁰ there may be decrease in the amplitude of the T waves with late inversion. In the acidosis of exercise or ammonium chloride ingestion¹⁰ there may be increase in the amplitude of the T waves. In both acidosis and alkalosis there may be a slight increase in the length of the Q-T interval. Changes in serum calcium levels have long been known to affect the electrocardiogram.^{11,12} The low levels seen in tetany¹² cause striking increases in the Q-T interval, while short Q-T intervals are found associated with the high blood calcium levels of hyperparathyroidism.¹³ Changes in serum potassium levels have also been demonstrated to affect the electrocardiogram, both in the experimental procedures in animals and in disease entities.^{4,7,14-19} Low levels of serum potassium seen in familial periodic paralysis,¹⁶ in diabetic acidosis,⁷ after injection of excessive amounts of desoxycorticosterone acetate,¹⁵ and in chronic nephritis¹⁷ cause low T waves in the electrocardiogram. High serum potassium levels found after injection of potassium^{4,14} or in nephritis¹⁹ may conversely be associated with high T waves. With higher levels of serum potassium in animals definite changes occur at certain concentrations: depression of the S-T segment at 8 to 10 milliequivalents per liter, intraventricular block at 10 milliequivalents per liter, disappearance of the P waves at 9 to 10 milliequivalents per liter, and, finally, cardiac arrest at 14 to 16 milliequivalents per liter.⁴ Increase in the length of the Q-T interval has also been correlated with low serum potassium levels.²⁰ The studies on the effect of magnesium on the electrocardiogram have been limited almost exclusively to high levels. Increases in serum magnesium in man and animals cause depression of conduction and depression of abnormal foci of irritability.^{21,22}

The relationship of the shifts of extracellular electrolytes to the changes in the intracellular electrolyte pattern is complex and largely an unexplored field. Yannet and Darrow²³ have shown in cats that changes in serum potassium levels are not always accompanied by proportional shifts in intracellular levels in muscle. Also, decreases in serum sodium concentrations are not accompanied by evidence of shift of water into the cells, or of loss of univalent base from the cells. In rats²⁴ sodium may partially replace potassium intracellularly in conditions of potassium depletion. In certain clinical states there appears to be a discrepancy between serum and intracellular levels. In familial periodic paralysis the serum potassium levels may be low, with postulated normal or increased intracellular levels as the urinary excretion decreases.²⁵ Further complicating this problem is the possible factor of lag in the balance between extra- and intracellular water and electrolytes.

In diabetic acidosis, before therapy, with lack of enough effective insulin, the problem arises concerning the nutrition of cardiac muscle. In the mammalian

heart-lung preparation, Barnes and associates²⁶ have shown that heart muscle is capable of direct oxidation of fat to the extent of at least two-thirds of its total metabolic requirement. Visscher and Muller²⁷ and Cruickshank²⁸ have also demonstrated in the heart-lung preparation that insulin is not necessary for the utilization of carbohydrate and does not increase glucose utilization. In rats, Evans²⁹ has shown that cardiac glycogen is not further increased by adding insulin to the glucose injection. These facts all suggest that cardiac nutrition may not be seriously altered during diabetic acidosis. The relationship of vitamin B to carbohydrate utilization in the muscle is well known. As many diabetic patients entering the hospital in acidosis show evidences of vitamin deficiency, this lack may contribute to nutritional changes in cardiac muscle. The relation of these changes to those observed in the electrocardiogram must remain speculative. Hypoglycemia has been shown to alter the electrocardiogram.³⁰ Suggested possible mechanisms are changes in blood pressure and coronary blood flow, cardiac glycogen, or serum potassium levels. As hypoglycemia was rarely present in our series, this factor cannot be considered significant in the serial changes in the electrocardiogram.

Anoxia experimentally produced in dogs³¹ causes changes in the height of the R wave due primarily to increase in the girth of the chest in expiration. Changes in the T waves appeared to be of cardiac origin. Serial changes in the height of the R wave were insignificant in our patients. More important is the fact that the serial changes in the electrocardiogram occurred whether shock was absent or present. The possibility of the effect on the electrocardiogram of waste products arising as a result of impaired renal function secondary to hemoconcentration and shock must be considered. In uremia, the electrocardiographic changes have been fairly well correlated with changes in serum electrolytes, particularly potassium, or with associated pericarditis. The electrocardiographic changes in diabetic acidosis are often most striking after the therapy of the first twenty-four hours, when the nonprotein nitrogen levels are usually normal. Also the serial changes occurred in patients who had no elevation of the nonprotein nitrogen.

The alterations caused by deep breathing and changes in diaphragm level³² may play a minor role. The changes found do not coincide well with those attributed to these factors. Many of the changes also occurred in patients following cessation of Kussmaul breathing. Abdominal distention also was not always present.

In the last analysis it is the state of the heart muscle which causes alterations in the electrocardiogram. What these intimate changes in the functional chemical state of the cardiac muscle are must remain speculative. That they are related in part to changes in the serum electrolytes has been demonstrated by this and other studies.

SUMMARY

Correlation of electrolyte and pH changes with serial electrocardiographic changes was made in thirteen patients during therapy for severe diabetic acidosis.

Sagging of the S-T segments was a prominent feature of the electrocardiogram on entry when acidosis was marked. This change usually disappeared within twenty-four hours. In nineteen instances of depressed S-T segment, the pH or carbon dioxide combining power was low in sixteen (84 per cent). However, in 31 per cent of the patients whose records showed isoelectric S-T segments, the pH or Carbon dioxide combining power was low. Experimentally, depression of the S-T segment occurs with moderate elevation of the serum potassium but there was no correlation in our series with changes in serum potassium levels. The etiology of this change requires further study.

Thirty-seven records showed prolonged Q-T intervals, many of these occurring one to four days after intensive therapy had been instituted. Sixteen (43 per cent) of these were associated with low total or ionized serum calcium or potassium. Twenty-one (57 per cent) of the patients whose records showed prolonged Q-T intervals had normal levels of serum calcium and potassium. There were seven patients in whom the Q-T interval was markedly prolonged; in six of these the serum calcium or potassium levels were below normal. These findings suggest that in some cases other factors than serum calcium and potassium depletion may be responsible for the prolongation of the Q-T interval.

There was a high degree of correlation between low T waves and low serum potassium levels. The T waves increased in amplitude with return of the potassium to normal or elevated levels.

The relationship of low serum magnesium to the electrocardiographic changes needs additional study.

The complex nature of the factors present in diabetic acidosis which may affect the myocardium is discussed. These factors include the relationship between extracellular and intracellular electrolytes, cardiac nutrition in acidosis and ketosis, and the effects of anoxia and azotemia.

REFERENCES

1. Bellet, Samuel, and Dyer, W. Wallace: The Electrocardiogram During and After Emergence From Diabetic Coma, *AM. HEART J.* 13:72, 1937.
2. Martin, Helen Eastman, and Wertman, Maxine: Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis, *J. Clin. Investigation* 26:217, 1947.
3. Ashman, Richard: The Normal Duration of the Q-T Interval, *AM. HEART J.* 23:522, 1942.
4. Winkler, Alexander W., Hoff, Hebbel E., and Smith, Paul K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, *Am. J. Physiol.* 124:478, 1938.
5. Harrop, George A., Jr., and Benedict, Ethel M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, *J. Biol. Chem.* 59:683, 1924.
6. Atchley, Dana W., Loeb, Robert F., Richards, Dickinson W., Jr., Benedict, Ethel M., and Driscoll, May E.: Diabetic Acidosis. A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, *J. Clin. Investigation* 12:297, 1933.
7. Holler, Jacob W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, *J. A. M. A.* 13:1186, 1946.
8. Briggs, A. P., Koechig, Irene, Doisy, Edward A., and Weber, Clarence J.: Some Changes in the Composition of Blood Due to the Injection of Insulin, *J. Biol. Chem.* 58:72, 1924.
9. Thompson, William Paul: The Electrocardiogram in the Hyperventilation Syndrome, *AM. HEART J.* 25:372, 1943.
10. Barker, Paul S., Shrader, Ethel, and Renzoni, Ethel: The Effects of Alkalosis and of Acidosis Upon the Human Electrocardiogram, *AM. HEART J.* 17:169, 1939.

11. White, Paul D., and Mudd, Seeley, G.: Observations on the Effect of Various Factor on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7:387, 1929.
12. Barker, Paul S., and Wilson, Frank N.: The Duration of Systole in Hypocalcemia, *AM. HEART J.* 14:82, 1937.
13. Kellogg, Frederick, and Kerr, W. J.: Electrocardiographic Changes in Hyperparathyroidism, *AM. HEART J.* 12:346, 1936.
- ✓ 14. Chamberlain, F. L., Scudder, J., and Zwemer, R. L.: Electrocardiographic Changes Associated With Experimental Alterations in Blood Potassium in Cats, *AM. HEART J.* 18:458, 1939.
15. Darrow, Daniel C., and Miller, Herbert C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate, *J. Clin. Investigation*, 21:601, 1942.
16. Stewart, Harold J., Smith, J. James, and Milherat, Ade T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, *Am. J. M. Sc.* 199:789, 1940.
- ✓ 17. Brown, Madelaine R., Currens, James H., and Marchand, John F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting From Potasisum Loss in Chronic Nephritis, *J. A. M. A.* 124:545, 1944.
18. Keith, Norman M., Burchell, H. B., and Baggenstoss, Archie A.: Electrocardiographic Changes in Uremia Associated With a High Concentration of Serum Potassium, *AM. HEART J.* 27:817, 1944.
19. Finch, Clement A., Sawyer, C. Glenn, and Flynn, John M.: Clinical Syndrome of Potassium Intoxication, *Am. J. Med.* 1:337, 1946.
20. Wofford, Charles I., and Ernstene, A. Carlton: The Diagnostic Significance of an Increased Q-T Interval in the Electrocardiogram, *Cleveland Clin. Quart.* 8:12, 1941.
- ✓ 21. Szekely, P.: The Action of Magnesium on the Heart, *Brit. Heart J.* 8:115, 1946.
22. Smith, Paul K., Winkler, Alexander W., and Hoff, Hebbel E.: Electrocardiographic Changes and Concentration of Magnesium in Serum Following Intravenous Injections of Magnesium Salts, *Am. J. Physiol.* 126:720, 1939.
23. Yannet, Herman, and Darrow, Daniel C.: The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle, Liver and Cardiac Muscle, *J. Biol. Chem.* 134:721, 1940.
- ✓ 24. Miller H. C., and Darrow, D. C.: Relation of Muscle Electrolyte to Alterations in Serum Potassium and to Toxic Effects of Injected Potassium Chloride, *Am. J. Physiol.* 130:747, 1940.
- ✓ 25. Allott, E. N., and McArdle, B.: Further Observations on Familial Periodic Paralysis, *Clin. Sc.* 3:229, 1938.
26. Barnes, R. H., MacKay, E. M., Mae, G. K., and Visscher, M. B.: The Utilization of Beta-Hydroxybutyric Acid by the Isolated Mammalian Heart and Lung, *Am. J. Physiol.* 123:272, 1938.
27. Visscher, Maurice B., and Muller, Erich A.: The Influence of Insulin Upon the Mammalian Heart, *J. Physiol.* 62:341, 1926.
28. Cruickshank, E. W. H.: Cardiac Metabolism, *Physiol. Rev.* 16:597, 1936.
29. Evans, Gerald: The Effect of Insulin on Cardiac and Liver Glycogen, *Am. J. Physiol.* 134:798, 1941.
- ✓ 30. Middleton, W. S., and Oatway, W. H.: Insulin Shock and the Myocardium, *Am. J. M. Sc.* 181:39, 1931.
- ✓ 31. Harris, A. Sidney, and Randall, Walter C.: Mechanisms Underlying Electrocardiographic Changes Observed in Anoxia, *Am. J. Physiol.* 142:452, 1944.
32. White, Paul D., Chamberlain, Francis L., and Graybill, Ashton: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart, *Brit. Heart J.* 3:233, 1941.

COMPARATIVE STUDY ON THE USE OF THE PURIFIED DIGITALIS GLYCOSIDES, DIGOXIN, DIGITOXIN, AND LANATOSIDE C, FOR THE MANAGEMENT OF AMBULATORY PATIENTS . WITH CONGESTIVE HEART FAILURE

ROBERT C. BATTERMAN, M.D., AND ARTHUR C. DEGRAFF, M.D.
NEW YORK, N. Y.

CONSIDERABLE attention has been focused upon the use of purified digitalis glycosides. There is no question that their use offers certain advantages over the digitalis leaf. Since the glycoside is a chemical entity, the physician is assured uniform potency regardless of the lot prescribed. In contrast to this, digitalis leaf must be submitted to controlled bio-assay, the results of which, although indicative of relative potency, cannot be directly applied to man.

As experience was gained in the use of the purified glycosides, it became evident that their potency, when used clinically, bore no relationship to the cat unit potency. If the latter was the basis of dosage, there was no way of predicting, except by clinical trial, whether a particular glycoside would produce results similar to that of digitalis leaf. Most likely severe toxicity would occur. It, therefore, became imperative that each glycoside should undergo extensive clinical trial in order to establish its relative potency and to determine satisfactory methods of dosage. In the hands of well-qualified cardiologists the use of purified glycosides offers no particular difficulty. However, unless precise directions are available and their pharmacology firmly established, the use of the purified glycosides by the general practitioner may not be satisfactory. It is for this reason that an extensive program for the evaluation of purified glycosides has been in progress by us and co-workers for the past ten years. Several reports¹ have already appeared on various phases of the glycoside problem, but to date we have avoided any reference to selection of any particular glycoside as the one of choice. This report deals with a comparative study of the use of the three glycosides, digoxin, digitoxin, and lanatoside C, in the treatment of the ambulatory patient.

The management of the patient with congestive heart failure may be considered as a twofold problem. The importance of the initial digitalization, regardless of the method used, is self-evident. However, in terms of digitalis potency or comparative potencies of the various glycosides, it is not the major problem. The patient can be readily digitalized, regardless of the potency of

From the Department of Therapeutics, New York University College of Medicine, and the New York University Cardiovascular Clinic.

Received for publication Jan. 31, 1947.

the preparation used, as long as repeated doses are administered. One should, of course, take into account absorbability and rapidity of dissipation of the digitalis preparation. Since, in our opinion, the maintenance of the digitalized state is the most important aspect of the management of the patient with congestive heart failure, this study was instituted to determine the following for each glycoside: (1) the daily undivided dose most likely to result in satisfactory maintenance; (2) the daily undivided dose most likely to result in minimal signs and symptoms of toxicity; (3) the therapeutic ratio; (4) the relative ease of establishment of satisfactory maintenance with control of congestive heart failure and ventricular rate; and (5) the ease of predicting the maintenance dose when initiating this dose in a patient who has been previously rapidly digitalized or who had been receiving another digitalis preparation.

SCOPE OF INVESTIGATION

The study was conducted on ambulatory patients. All required the daily administration of a digitalis preparation to be maintained in a state of satisfactory compensation. The cessation of digitalis, therefore, or improper maintenance would immediately result in the development of signs and symptoms of congestive heart failure. None of the patients required supplementary diuretic therapy, and if at any time their use became necessary, the patient was no longer followed for maintenance studies. Seventy-four patients, diagnosed according to the criteria of the New York Heart Association,² composed the study group. The diagnostic data are presented in Table I. Patients with recent

TABLE I. DIAGNOSIS AND HEART RHYTHMS OF AMBULATORY PATIENTS TREATED WITH GLYCOSIDES

	NUMBER OF PATIENTS
Diagnosis	
Rheumatic heart disease	38
Mitral stenosis and insufficiency	28
Mitral stenosis and insufficiency and aortic insufficiency	6
Mitral stenosis and insufficiency and aortic stenosis and insufficiency	4
Arteriosclerotic heart disease	13
Arteriosclerotic and hypertensive heart disease	10
Hypertensive heart disease	5
Syphilitic heart disease	2
Rheumatic and hypertensive heart disease	1
Unknown heart disease	2
Unknown and hypertensive heart disease	1
Unknown and hyperthyroid heart disease	2
Total	74
Rhythm	
Auricular fibrillation	52
Normal sinus rhythm	22
Total	74

myocardial infarction, with frequent episodes of anginal syndrome, or other medical conditions which may have either altered the cardiac status or interfered with proper evaluation of therapy were excluded.

METHOD

With few exceptions, the patients had been previously observed for months or years on a standard digitalis leaf preparation (U. S. P. X to XII) so that their digitalis requirements were well known. The initial dose level of the glycoside* substituted for the digitalis leaf was arbitrarily chosen as any multiple of the smallest tablet furnished by the pharmaceutical concern. Regardless of the dose, the patient was advised to take the entire amount as an undivided dose, preferably at the same time each day. As experience was gained in the use of glycosides, it became evident that this was very important for proper maintenance. A division of the dose over a twelve- to sixteen-hour period would have resulted in accentuation of the dissipation factor which interfered with proper evaluation of the dose level. A supply of the glycoside was dispensed at each clinic visit to last until the next examination. The visits were at intervals of between two and five weeks but were usually at intervals of three weeks. If the patient failed to keep an appointment or if the dose of the glycoside was not taken regularly, the trial was discarded and a new period of observation begun. A minimum period of eight weeks of observation on each dose level was established because it became evident that it might require this time for the full cumulative effects of single daily doses to achieve maximum action. The patient was, therefore, observed for a trial period of at least eight to ten weeks, usually three clinic visits, on each dose level. The only exception to this rule was when a particular dose resulted in toxicity or was definitely unsatisfactory for maintenance and the patient's welfare demanded an immediate change of dosage. At the end of a suitable period of observation, an electrocardiogram was taken and another dose level instituted. An attempt was made to determine the minimal dose for either satisfactory maintenance or developments of signs and symptoms of toxicity by either decreasing or increasing the daily dose by small increments.

RESULT

It was possible to evaluate digoxin for a total of 119 trials in forty patients; digitoxin for 103 trials in thirty-two patients, and lanatoside C for 133 trials in forty-six patients. The number of patients receiving each glycoside or combination of glycosides is presented in Table II. We were fortunate in being able to follow sixteen patients over a sufficient length of time to allow studies on all three glycosides. Complete studies with establishment of both minimal maintenance and toxic doses are available in ten of these patients.

**Digoxin* was supplied by Burroughs Wellcome & Co., Inc., New York, N. Y., in 0.25 mg. tablets. *Digitoxin* was supplied by Varick Pharmacal Co., Inc., New York, N. Y., under the trade name *Digitatine Nativelle*, in tablets of 0.1 and 0.2 mg. *Lanatoside C* was supplied by Sandoz Chemical Works, Inc., New York, N. Y., under the trade name *Cedilanid*, in 0.5 mg. tablets.

TABLE II. NUMBER OF PATIENTS TREATED WITH EACH GLYCOSIDE OR COMBINATION OF GLYCOSIDES

Total number of patients	74
Patients receiving digoxin	40
Established maintenance dose	30
Established toxic dose	28
Established both	22
Patients receiving lanatoside C	46
Established maintenance dose	34
Established toxic dose	34
Established both	27
Patients receiving digitoxin (Digitaline Nativelle)	32
Established maintenance dose	26
Established toxic dose	31
Established both	26
Patients receiving all three glycosides	16
Complete studies available	10
Comparisons of maintenance dose	12
Comparisons of toxic dose	13
Patients receiving digoxin and lanatoside C	25
Complete studies available	15
Comparisons of maintenance dose	17
Comparisons of toxic dose	19
Patients receiving digoxin and digitoxin	20
Complete studies available	14
Comparisons of maintenance dose	17
Comparisons of toxic dose	17
Patients receiving lanatoside C and digitoxin	16
Complete studies available	12
Comparisons of maintenance dose	13
Comparisons of toxic dose	14

TABLE III. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF DIGOXIN

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.25	17	9	5	3	0
0.5	30	15	6	7	2
0.75	29	11	4	5	9
1.00	20	13	3	0	4
1.25	12	5	1	0	6
1.5	7	3	0	0	4
1.75	3	1	0	0	2
2.0	1	0	0	0	1
Total	119	57	19	15	28

Studies With Digoxin.—Experiences with the various dose levels are summarized in Table III. It is apparent that there is considerable individual variation. A daily undivided dose of 1.0 mg. would have resulted in toxicity in fifteen of thirty-one patients (48.4 per cent), but in sixteen of twenty patients in whom this dose was tried, maintenance was satisfactory. The maintenance dose of digoxin was established in thirty patients (Table IV) and ranged be-

TABLE IV. DAILY UNDIVIDED DOSE OF DIGOXIN REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.25	9	
0.50	7	2
0.75	5	9
1.00	6	4
1.25	2	6
1.50	1	4
1.75	0	2
2.00	0	1
Total	30	28

○—○ MAINTENANCE

○---○ TOXICITY

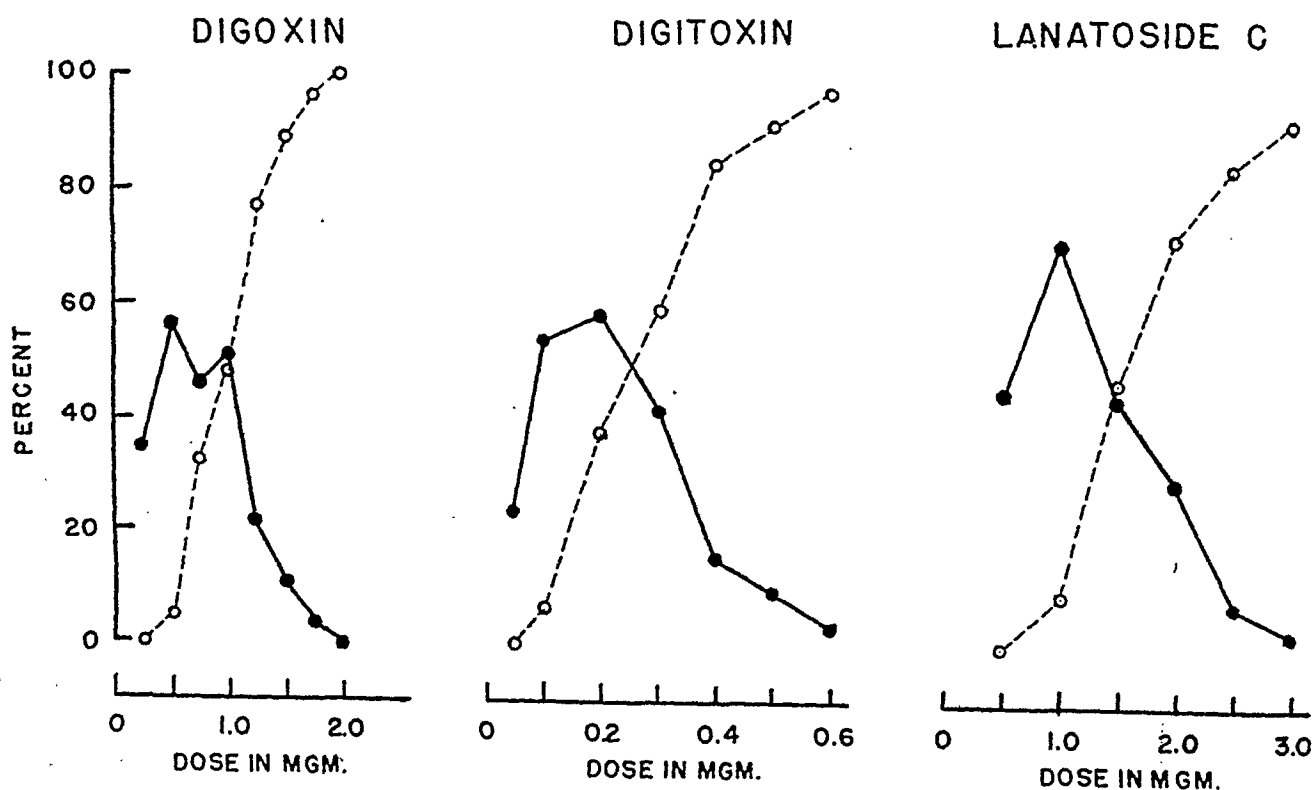


Fig. 1.—Per cent of patients presenting either maintenance or toxicity with the daily administration of various doses of digoxin, digitoxin, and lanatoside C.

tween 0.25 and 1.5 mg., the dose roughly paralleling the severity of the underlying heart disease. Seventy per cent of the patients were maintained with a dose of 0.75 mg. or less. The toxic dose for daily administration ranged between 0.5 and 2.0 mg. and was established in twenty-eight patients (Table IV). Approximately 60 per cent of the patients had toxicity with an undivided dose of 1.0 mg. or above. Fig. 1 represents the predictability of achieving maintenance or toxicity with any daily dose level and indicates that the dose of choice when initiating maintenance with digoxin, if no knowledge of previous digitalis leaf dosage is available, is 0.5 milligrams. This dose will be effective in the greatest number of patients with the least possibility of toxicity. A daily undivided dose of 1.0 mg. has an equal chance of either maintaining the patient or producing toxicity. If the patient has been previously receiving digitalis leaf, digoxin could be substituted in doses of 0.5 mg. for each 0.1 Gm. of digitalis leaf (U. S. P. XII). In all cases the minimal maintenance dose was established without difficulty. This was accomplished in spite of the rapid dissipation of digoxin. The latter interfered with proper maintenance only if the daily dose was divided.

Studies With Digitoxin.—Results with digitoxin are summarized in Tables V and VI and Fig. 1. Fifty per cent of the patients were maintained with a daily dose of 0.1 mg. or less. The toxic daily dose was noted from 0.1 mg. upward but was usually encountered above 0.2 milligram. Thus, approximately 61 per cent of the patients manifested toxicity with a dose of 0.3 mg. or above. As in the case of the other glycosides, considerable individual variation was noted. The maintenance dose ranged between 0.05 and 0.3 milligram. The dose which appears to be the best for selection when the patient requires maintenance for the first time would be 0.1 milligram. This dose will maintain the majority of the patients, while the likelihood of toxicity is very small. The daily administration of 0.2 mg. resulted in toxicity in 37.5 per cent of the pa-

TABLE V. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF DIGITOXIN

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.05	10	6	1	3	0
0.1	23	11	3	7	2
0.2	29	15	3	1	10
0.3	20	12	1	0	7
0.4	13	4	1	0	8
0.5	5	3	0	0	2
0.6	3	1	0	0	2
Total	103	52	9	11	31

TABLE VI. DAILY DOSE OF DIGITOXIN REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.05	6	0
0.1	7	2
0.2	11	10
0.3	2	7
0.4	0	8
0.5	0	2
0.6	0	2
Total	26	31

tients. The maintenance and toxic doses were established without any difficulty with the exception of one patient who could not tolerate any dose. The smallest size tablet used was 0.1 milligram. With the administration of 0.1 mg. every other day (0.05 mg. per day), adequate maintenance was obtained in seven patients (24 per cent). It is, therefore, recommended that digitoxin should be made available in 0.05 mg. tablets.

Studies With Lanatoside C.—Results with lanatoside C are summarized in Tables VII and VIII and Fig. 1. The maintenance dose ranged between 0.5 and 3.0 milligrams. Approximately 62 per cent of the patients were maintained with a daily undivided dose of 1.0 milligram. Toxic effects were noted with 1.0 mg. or more and were usually encountered with a dose greater than 1.5 mg., toxicity occurring in 28 per cent of the patients with this dose or above. Again, there was considerable overlapping of doses and individual variations. This was particularly so for the 1.5 mg. dose. From Fig. 1 it can be seen that there is an equal chance of either producing maintenance or toxicity with this dose.

TABLE VII. EFFECTIVENESS OF VARIOUS DAILY ORAL DOSES OF LANATOSIDE C

DOSE (MG.)	TRIALS	NUMBER OF PATIENTS			
		WELL MAINTAINED	FAIRLY WELL MAINTAINED	DEVELOPED INCREASED CONGESTIVE HEART FAILURE	DEVELOPED TOXICITY
0.5	27	12	4	11	0
1.0	39	20	5	10	4
1.5	35	10	6	5	14
2.0	20	9	1	1	9
2.5	8	3	0	1	4
3.0	4	1	0	0	3
Total	133	55	16	28	34

TABLE VIII. DAILY UNDIVIDED DOSES OF LANATOSIDE C REQUIRED FOR EITHER MAINTENANCE OR TOXICITY

DOSE (MG.)	NUMBER OF PATIENTS	
	MAINTENANCE	TOXICITY
0.5	12	0
1.0	9	4
1.5	6	14
2.0	5	10
2.5	1	3
3.0	1	3
Total	34	34

The most satisfactory dose for initiating maintenance would be 1.0 mg. daily. It was definitely more difficult to establish a maintenance dose with lanatoside C than with the other glycosides. This was reflected in the relatively higher number of trials, 21 per cent of which resulted in congestive heart failure as compared with 12.6 per cent and 10.7 per cent for digoxin and digitoxin, respectively (Table X). In seven patients establishment of the maintenance dose was particularly difficult since the patients were in congestive heart failure with one dosage level and developed toxicity with the next dosage level. In several instances the patient's condition did not allow further studies with lanatoside C since it was obvious that the maintenance dose would not be established with any degree of certainty in a suitable period of time to benefit the patient. In such cases it became necessary to change to digitalis leaf or another glycoside.

Comparative Studies in the Same Patient.—Complete studies for maintenance and toxicity dose for all three glycosides are available on ten patients. These are summarized in Table IX. In general, the relative potency for each glycoside was the same for each patient. If the patient could be maintained with a small dose of one glycoside, the patient could be maintained with a small dose of the other two glycosides. The same relative potency held also for the toxic dose. With one exception (Patient S. S.) the therapeutic range of all glycosides was not too dissimilar.

Therapeutic Ratio.—The therapeutic ratios for the three glycosides were identical. When the minimal maintenance dose was doubled, toxicity occurred with digoxin in 63.6 per cent of the patients, with digitoxin in 65.4 per cent, and with lanatoside C in 62.9 per cent.

Toxic Manifestations.—With daily doses that produced toxicity, the signs and symptoms were the same for all three glycosides as far as type and incidence were concerned. They differed from those noted with digitalis leaf in two respects. It was unusual for diarrhea to be noted as a toxic symptom for any of the glycosides. Visual disturbances were just as common but did not include yellow or green vision. Occasional patients noted alteration in color vision with

emphasis on objects appearing white. Although the impression was gained that gastrointestinal irritation was less with the use of the glycosides, it is impossible for us to state with certainty that this is significant. In our experience the usual small doses of digitalis leaf administered for maintenance rarely result in true gastrointestinal irritation. If a patient develops nausea and vomiting with digitalis leaf, it is invariably the result of central toxicity and the same symptoms would occur for each glycoside if comparable doses were administered.

TABLE IX. COMPARATIVE DAILY MAINTENANCE AND TOXIC DOSES IN THE SAME PATIENT FOR DIGOXIN, DIGITOXIN, AND LANATOSIDE C

PATIENT	DIGOXIN		DIGITOXIN		LANATOSIDE C	
	M. D.* (MG.)	T. D.† (MG.)	M. D. (MG.)	T. D. (MG.)	M. D. (MG.)	T. D. (MG.)
J. M.	1.0	1.5	0.2	0.4	2.0	2.5
S. S.	0.25	0.75	0.05	0.2	1.5	1.5
F. L.	1.0	2.0	0.2	0.3	1.5	2.0
N. P.	0.25	0.75	0.1	0.4	1.0	2.0
C. S.	0.5	0.75	0.1	0.2	1.5	2.0
F. B.	0.75	1.75	0.2	0.5	1.5	2.5
G. G.	0.25	0.75	0.1	0.2	0.5	1.5
A. H.	0.25	0.5	0.05	0.1	0.5	1.5
M. M.	1.0	1.25	0.1	0.2	2.0	2.5
Z. P.	0.5	0.75	0.2	0.2	1.0	2.0

*M. D., Maintenance dose.

†T. D., Toxic dose.

TABLE X. COMPARATIVE SUMMARY OF THE AMBULATORY USE OF DIGOXIN, DIGITOXIN, AND LANATOSIDE C

	DIGOXIN	DIGITOXIN	LANATOSIDE C
Daily undivided dose most likely resulting in maintenance	0.5 mg.	0.1 mg.	1.0 mg.
Daily undivided dose most likely resulting in toxicity	1.0 mg.	0.2-0.3 mg.	1.5-2.0 mg.
Patients presenting toxicity on doubling minimal maintenance dose	63.6%	65.4%	62.9%
Number of trials resulting in poor maintenance regardless of dose	12.6%	10.7%	21%
Ease of achieving maintenance	Good	Good	Fair
Ease of predicting dose	Good	Good	Trial and error
Dissipation	Rapid	Slow	Rapid
Duration of Toxicity	Short	Long	Short

The glycosides differed, however, in the duration of toxicity. Whereas it was unusual for the signs and symptoms of toxicity to persist longer than forty-eight hours for either digoxin or lanatoside C; in many instances the toxicity following digitoxin persisted for seventy-two to ninety-six hours or even a week. Furthermore, in adjusting the dose of the glycoside following the occurrence of

toxicity, it was absolutely imperative to stop the administration of digitoxin for several days. In the case of lanatoside C or digoxin, the patient could easily continue on a smaller dose or even the same total dose, but in divided amounts, and yet have all signs and symptoms of toxicity subside very promptly.

DISCUSSION

The most important advantage of the introduction of purified digitalis glycosides is their uniformity from lot to lot. The physician is assured that the potency of any glycosides will always be the same and that maintenance, when established, will not vary because of uncontrolled factors inherent in the preparation.

With the exception of an occasional patient who cannot tolerate digitalis leaf because of local gastrointestinal irritation and the psychologic factor of prescribing digitalis, the use of the purified glycosides does not offer any other advantage over digitalis leaf. Purified glycosides will not result in a more efficient or safer digitalization. The patient will not be maintained any more effectively. If a patient is no longer satisfactorily maintained with digitalis leaf and toxicity occurs with the next dosage level, the substitution of a purified glycoside will result in the same response if comparable doses are used. In other words, the glycosides may vary in terms of latency of action, speed of dissipation, and degree of gastrointestinal absorption, but they appear to be identical as far as their action upon improving the efficiency of heart muscle is concerned. Furthermore, the toxic manifestations, although differing in duration, appear to be generally the same for the purified glycosides and digitalis leaf.

In comparing any particular glycoside with any other, the same relative potencies held for both maintenance and toxic doses. The therapeutic range for each preparation appears to be the same. However, in the case of lanatoside C, the therapeutic range in some instances appears to be exceedingly small. This is related to factors other than cardiac action and may be explained either by rapidity of dissipation or destruction of the drug in the gastrointestinal tract or by a combination of both of these factors. Evidence in favor of destruction is the relative difficulty encountered in determining the maintenance dose of lanatoside C in respect to digoxin; dissipation studies³ of both of these glycosides in man are similar. Furthermore, knowing the maintenance dose of digitalis leaf, digitoxin, or digoxin, it was comparatively easy to predict the maintenance dose or interchange of any three of these preparations, whereas for lanatoside C it was a question of trial and error in many cases. This definitely impairs the usefulness of lanatoside C for oral use in maintenance. The usefulness of digitoxin, while satisfactory for maintenance, is offset by its slow rate of dissipation and prolonged toxicity. Furthermore, the dosage forms that are supplied at present, 0.1 and 0.2 mg., do not lend themselves to great freedom in establishing satisfactory maintenance levels. An increase of 100 per cent in dosage of digitoxin is relatively more dangerous than the same increase of digoxin or lanatoside C. For these reasons digoxin appears to be the glycoside of choice for the daily management of the patient with congestive heart failure.

SUMMARY

1. Comparative studies on three purified digitalis glycosides, digoxin, digitoxin, and lanatoside C, were performed in a group of seventy-four ambulatory patients.

2. For reasons of safety in administration and satisfactory maintenance, digoxin is the glycoside of choice.

3. Lanatoside C administered orally is not satisfactory for the routine daily management of the patient with congestive heart failure.

4. Other than the assurance of obtaining uniformity in various lots, the glycosides have no particular advantage over digitalis leaf.

5. The incidence and degree of toxic symptoms is the same for the three glycosides. The duration of toxicity is much greater with digitoxin than with lanatoside C or digoxin.

This study was made possible by the fullest cooperation, financial assistance, and generous supplies of the glycosides by the following Pharmaceutical Companies: Burroughs Wellcome & Co. (U.S.A.) Inc., New York, N. Y.; Lederle Laboratory Division, American Cyanamid Co., Pearl River, N. Y.; Sandoz Chemical Works, Inc., New York, N. Y.; and Varick Pharmacal Co., Inc., New York, N. Y.

REFERENCES

1. (a) Batterman, R. C., Rose, O. A., and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, *AM. HEART J.* 20: 443, 1940.
- (b) Batterman, R. C., Holman, D. V., and DeGraff, A. C.: The Therapeutic Effectiveness of Potency of Digilanid in the Treatment of Congestive Heart Failure, *Ann. Int. Med.* 14:2058, 1941.
- (c) DeGraff, A. C., and Batterman, R. C.: Recent Advances in Digitalis Therapy With Particular Attention to the Use of Pure Glycosides, *M. Clin. North America*, 26:929, 1942.
- (d) Rose, O. A., Batterman, R. C., and DeGraff, A. C.: Clinical Studies on Digoxin, a Purified Digitalis Glycoside, *AM. HEART J.* 24:425, 1942.
- (e) Eichna, L. W., Taube, H., and DeGraff, A. C.: Serial Determinations of Cardiac Output (Ballistocardiogram) and Electrocardiogram in Normal Man After the Intravenous Administration of Purified Cardiac Glycosides, *J. Pharmacol. & Exper. Therap.* 78:22, 1943.
- (f) Eichna, L. W., and Taube, H.: A Comparison of the Actions of Four Cardiac Glycosides on a Patient With Congestive Heart Failure, *AM. HEART J.* 26:631, 1943.
- (g) Eichna, L. W., and Taube, H.: The Effect of Intravenously Administered Digoxin and Ouabain on the Systemic Venous Pressure of Patients With Congestive Heart Failure, *AM. HEART J.* 27:641, 1944.
- (h) Batterman, R. C., and DeGraff, A. C.: Studies on the Rate of Dissipation and Digoxin in Man, *Federation Proc.* 4:112, 1945.
- (i) DeGraff, A. C.: Clinical Comparison of the Cardiac Glycosides, *New York State J. Med.* 45:1803, 1946.
2. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York Heart Association, New York, 1939.
3. Unpublished data.

ELECTROCARDIOGRAPHIC CHANGES IN EARLY SYPHILIS

HOWARD P. STEIGER, M.D.,* CHARLOTTE, N. C., AND JOSEPH EDEIKEN, M.D.†
PHILADELPHIA, PA.

IT IS well known that there is a spirochetemia during the early stages of a syphilitic infection. There is, however, considerable difference of opinion as to whether or not the heart is affected during this period. Extensive investigations have been made and the conclusion in most of the later studies is that there is little evidence of cardiovascular involvement in early syphilis.¹⁻⁶ The majority of these analyses does not include electrocardiographic studies of the dark-field positive patient before, during, and after treatment. In those cases studied during the course of intensive treatment, the electrocardiographic changes when present were, in most cases, attributed to the toxic effects of the arsenicals upon the myocardium.

Since penicillin shows little evidence of being toxic to the myocardium, and, at the same time, the patients are hospitalized for complete syphilitic treatment, we think the entire subject should be re-evaluated.

Grassmann⁷ in 1900 described cardiac arrhythmias and murmurs in patients in various stages of syphilis, and since many of these changes were present prior to treatment and cleared following therapy, they were considered to be due to syphilis. In 1913, Warthin⁸ reported finding *Treponema pallidum* in the myocardium of cases of active secondary syphilis. His description of these findings is indeed classic: "Large colonies of spirochetes may be found in the myocardium either in the tissue spaces of certain muscle areas, or about the blood vessels, without any changes in the neighboring heart muscle that can be recognized by any technical methods at the present time. The muscle stains as well as normal heart muscle; it contains no vacuoles or granules and presents all the appearances of normal muscle. The spirochetes lie in the intermuscular spaces, often in great numbers. Sometimes they appear within the muscle substance,

This study is part of the investigations on penicillin in syphilis being conducted under Grant RG-13C from the National Institute of Health. The work is collaborated in and sponsored by the Institute for the Study of Venereal Disease, University of Pennsylvania and U. S. Public Health Service co-operating; by the members of the Penicillin-Syphilis Panel, including Herman Beerman, M.D., George D. Gammon, M.D., Paul Gyorgy, M.D., Norman R. Ingraham, Jr., M.D., John W. Lentz, M.D., William O. LaMotte, M.D., E. K. Rose, M.D., and John H. Stokes, M.D., Director and responsible investigator, and the Edward B. Robinette Foundation, and the Medical Clinic, Hospital of the University of Pennsylvania.

An abstract of this paper was presented at a Symposium on Recent Advances in the Investigation of Venereal Diseases held in Washington, D. C. on April 17, 1947, under the auspices of the Syphilis Study Section of the National Institute of Health.

Received for publication Jan. 14, 1947.

*P. A. Surgeon (R), U. S. Public Health Service.

†Instructor, Department of Medicine, University of Pennsylvania Medical School.

as shown in cross sections, but this is not common. Such findings are most frequent in congenital syphilis, but such collections of spirochetes without recognizable myocardial changes are found in acquired syphilis, particularly in active secondary and early tertiary syphilis."⁹ Boyd,⁵ however, states that myocardial scars and focal collections of lymphocytes and plasma cells have been attributed to syphilis, but without justification.

Turner and White⁶ studied fifty cases of primary and secondary syphilis; forty-nine of these showed normal findings or minor variations which could not be ascribed to any pathologic process. The one case showing changes revealed left axis deviation and rather high P waves in Leads II and III. No significant T-wave changes were found. They concluded that the evidence of cardiovascular involvement in early syphilis was exceedingly rare. On reviewing these cases, however, one is impressed with the fact that all of the cases had received some arsenotherapy prior to the electrocardiographic examination, and that studies were not made for at least two weeks after treatment started. In light of the transient nature of the changes often noted in the study described herewith, it seems entirely possible that these patients were studied after the time during which these changes could have occurred. Arnett¹ reported no significant findings in twenty-four cases of secondary syphilis, but it is not clear as to the amount of treatment these patients had received prior to the electrocardiographic examination. The time interval between treatment and examination also is not stated. Chamberlain and Follows³ reported fifty-seven cases of early syphilis studied from the cardiac standpoint and found no evidence of myocardial change. Again the question of treatment prior to examination must be raised. Wilson and associates² studied twenty cases of primary and secondary syphilis before and after salvarsan and noted no clinical or electrocardiographic evidence of cardiac or aortic involvement. He concluded that recognizable involvement of these organs in early stages of the disease is rare.

Sadusk,¹⁰ in discussing the papers of Leifer and associates and Elliott and associates on massive arsenotherapy, reported inversion of T_3 and diminished amplitude of T_2 in a few cases treated with the five-day arsenoxide drip. Geiger, Craig, and Sadusk¹¹ described electrocardiographic changes in twenty-one of twenty-five cases (including two cases retreated). These patients, treated with the five-day drip, showed electrocardiographic changes similar to those of this study, except they were not noted prior to treatment. These changes were considered to be toxic manifestations of arsenic and not due to syphilis. Three cases that had received previous arsenotherapy in this series did not show the T-wave changes. Stokes, Beerman, and Ingraham, Jr.,¹² state that as methods for the detection of conduction defects improve, an increased frequency of changes is noted; but whether this increase is due to lesions or disturbances produced by ischemic fibrosis or active spirochete-containing foci is still over the horizon. Klotz and Crede¹³ in a series of 100 consecutive cases of primary and secondary syphilis treated with the twenty-day syringe method (approximately 60 mg. of mapharsen daily for twenty days) found four cases with altered T waves when examinations were made before treatment. These abnormalities disappeared following the twenty days of arsenotherapy. Six additional cases

showed low voltage T waves which increased in amplitude at the completion of arsenotherapy. Other minor changes such as ventricular extrasystoles and slightly depressed RS-T segments were noted.

METHOD AND PROCEDURE

Only cases of primary and secondary syphilis with dark-field positive lesions confirmed by at least two experts were selected (Table I). Individuals with a history of heart disease, hypertension, and diabetes were not included. The patients

TABLE I. SUMMARY OF THIRTY CASES OF EARLY SYPHILIS STUDIED. ALL CASES DARK-FIELD POSITIVE FOR *TREPONEMA PALLIDUM*

NO.	ELECTROCARDIOGRAPHIC ABNORMALITY*		DIAGNOSIS	REMARKS
	BEFORE TREATMENT	DURING TREATMENT		
1	None	Definite	Secondary	Abnormal 7th day† only. See Fig. 1
2	None	None	Secondary	Normal throughout
3	Definite	Definite	Secondary	Varied abnormal to normal for 112 days; normal at 162 days. See Fig. 5
4	Definite	Definite	Secondary relapse	Abnormal 30 days
5	None	None	Seropositive primary	Normal throughout
6	None	Definite	Secondary relapse	Abnormal 3rd to 6th day
7	None	None	Secondary relapse	Normal throughout
8	Definite	Definite	Secondary	Abnormal to 58th day; then normal to 77th
9	None	None	Secondary	Normal throughout
10	None	Definite	Secondary reinfection (?)	Abnormal 3rd day only
11	Definite	Definite	Seronegative primary	Abnormal for 35 days. See Fig. 3
12	None	None	Secondary	Normal throughout
13	None	None	Secondary	Normal throughout
14	Definite	Definite	Secondary	Still abnormal at 97 days. See Fig. 4
15	None	None	Secondary relapse	Normal throughout
16	None	None	Secondary relapse	Normal throughout
17	Definite	Not done	Secondary	No follow-up
18	Questionable	Questionable	Secondary relapse	Low amplitude T waves only
19	Definite	Definite	Seropositive primary	Normal in 11 days. See Fig. 2
20	None	None	Secondary	Normal throughout
21	None	Definite	Secondary relapse	Abnormal 5th day only
22	None	None	Secondary	Normal throughout
23	None	None	Secondary	Normal throughout
24	None	None	Secondary	Normal throughout
25	None	None	Secondary relapse	Normal throughout
26	Definite	Definite	Seronegative primary	Improved 3rd day, regressed on 8th, normal on 30th day
27	Definite	None	Secondary	Abnormal only before treatment
28	Definite	Definite	Secondary relapse	Abnormal throughout
29	Questionable	Questionable	Secondary	Still has low amplitude T waves at 55 days
30	Definite	Definite	Secondary	Abnormal throughout

*For criteria of abnormality see page 677.

†Day—first day of treatment counted as first day.

were hospitalized during treatment and were completely studied from a general standpoint as well as from the cardiologic standpoint prior to treatment and during treatment. The electrocardiograms were taken prior to the institution of penicillin therapy and as near to every three days thereafter as administratively possible. All electrocardiographic determinations were taken with the patient in a sitting position. With the exception of one case who received calcium penicillin in beeswax peanut oil, all patients received penicillin sodium dissolved in normal saline without the addition of procaine. This was given in the gluteal muscle every three hours night and day. The controls were patients with no physical, serologic, or historical evidence of syphilis. These individuals had minor pyogenic infections such as impetigo, etc., and received the same amounts of penicillin as the syphilitic patients.

STUDIES AND OBSERVATIONS

The electrocardiographic abnormalities consisted of T-wave and RS-T segment changes in the limb and/or chest leads; in no instance was there any evidence of interference in conduction.

In addition to inverted and diphasic T waves in Leads I and/or II, T waves in these leads were considered abnormal when upright, but less than 1 mm. in amplitude; in the chest leads, upright T waves less than 2 mm. in amplitude were considered abnormal. The RS-T segment was considered abnormal in the limb leads when displaced upward or downward more than 2 mm.; such changes were common in the chest leads, although as an isolated finding they were not considered abnormal inasmuch as such changes, especially elevation of the RS-T segment, are frequently observed in supposedly normal individuals. A Q_3 wave as an isolated finding was not considered abnormal.

Fifteen (50 per cent) of thirty cases showed abnormalities either before or during treatment; of these, eleven showed definite changes before the start of penicillin treatment and the remainder during treatment. In nine cases the changes involved the T waves in Leads I and II and the chest leads, although in some the abnormalities varied from tracing to tracing, and in three instances the T waves in Lead I were inverted. In three cases T_2 alone showed the most marked abnormality, and in all three the changes were of short duration. In one instance abnormalities were observed in T_2 and the chest leads, and in two cases the chest leads alone disclosed changes. In eight cases the electrocardiogram was observed to return to normal in a period ranging from three days to four months. In one instance (not observed to return to normal after two months) follow-up was not possible because the patient, an English seaman, was forced to leave the country. In those who had showed electrocardiographic abnormalities before treatment, examination failed to reveal any other cause for these changes. The electrocardiographic abnormalities were of several types:

1. In four instances the changes were fleeting (Fig. 1). The T-wave abnormalities were present during only one examination, and it is, therefore, possible that if electrocardiograms were made more frequently than every third

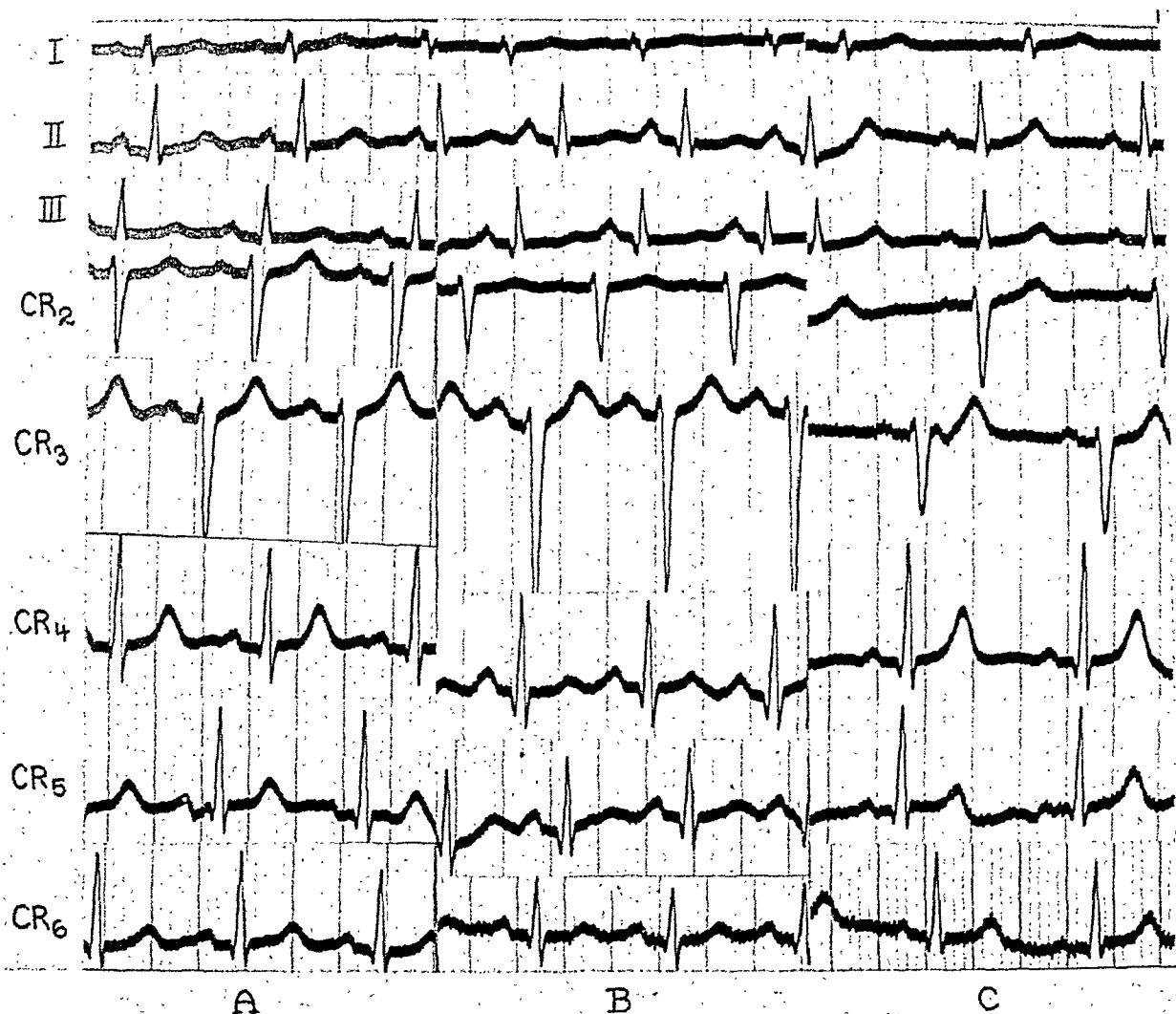


Fig. 1.—Case 1. A, Electrocardiogram of white woman, 27 years of age, with secondary syphilis, taken May 29, 1946, before treatment. B, Tracing made June 5, 1946, after receiving 1,280,000 units of penicillin. C, Tracing made June 8, 1946. Subsequent electrocardiograms showed no changes.

day, a larger percentage of cases may have shown changes. In another case, (Fig. 2) the T-wave abnormalities were present before treatment, and returned to normal within a period of eleven days.

2. Variation in T-wave abnormalities in the same leads were present during repeated examinations as shown in Fig. 3.

3. The leads in which T-wave abnormalities appeared varied in repeated examinations. See Fig. 4.

In an effort to determine whether a particular type of case showed electrocardiographic changes, the available material was analyzed further as follows:

Herxheimer Reaction.—It is admitted that other evidences of the Herxheimer reaction or therapeutic shock could occur without temperature elevation or skin manifestations. These reactions, however, were the only evidence used as criteria of Herxheimer reactions in this series.

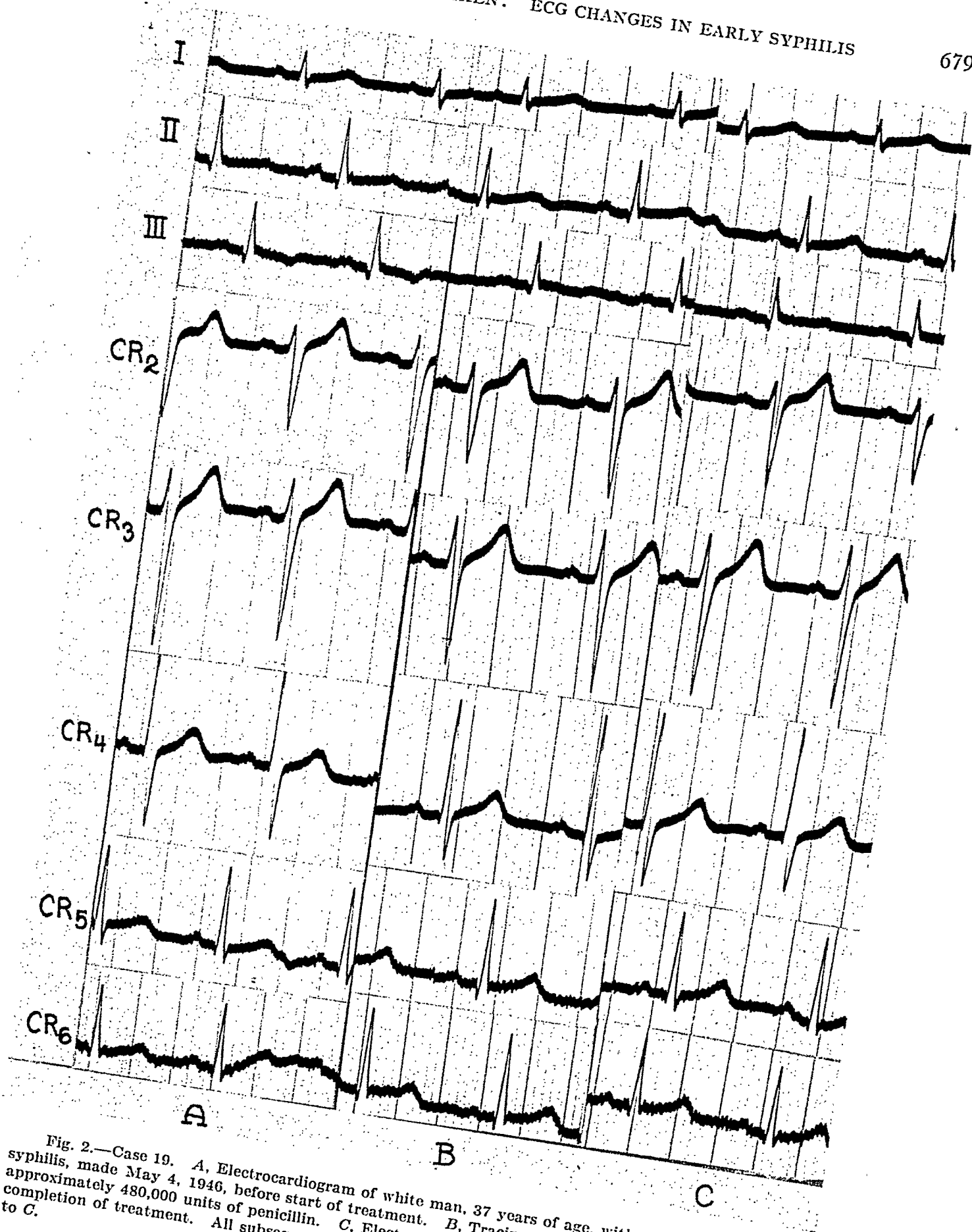


Fig. 2.—Case 19. A, Electrocardiogram of white man, 37 years of age, with seropositive primary syphilis, made May 4, 1946, before start of treatment. B, Tracing made May 7, 1946, after receiving approximately 480,000 units of penicillin. C, Electrocardiograms made May 14, 1946, two days after completion of treatment. All subsequent tracings including those made on readmissions were similar to C.

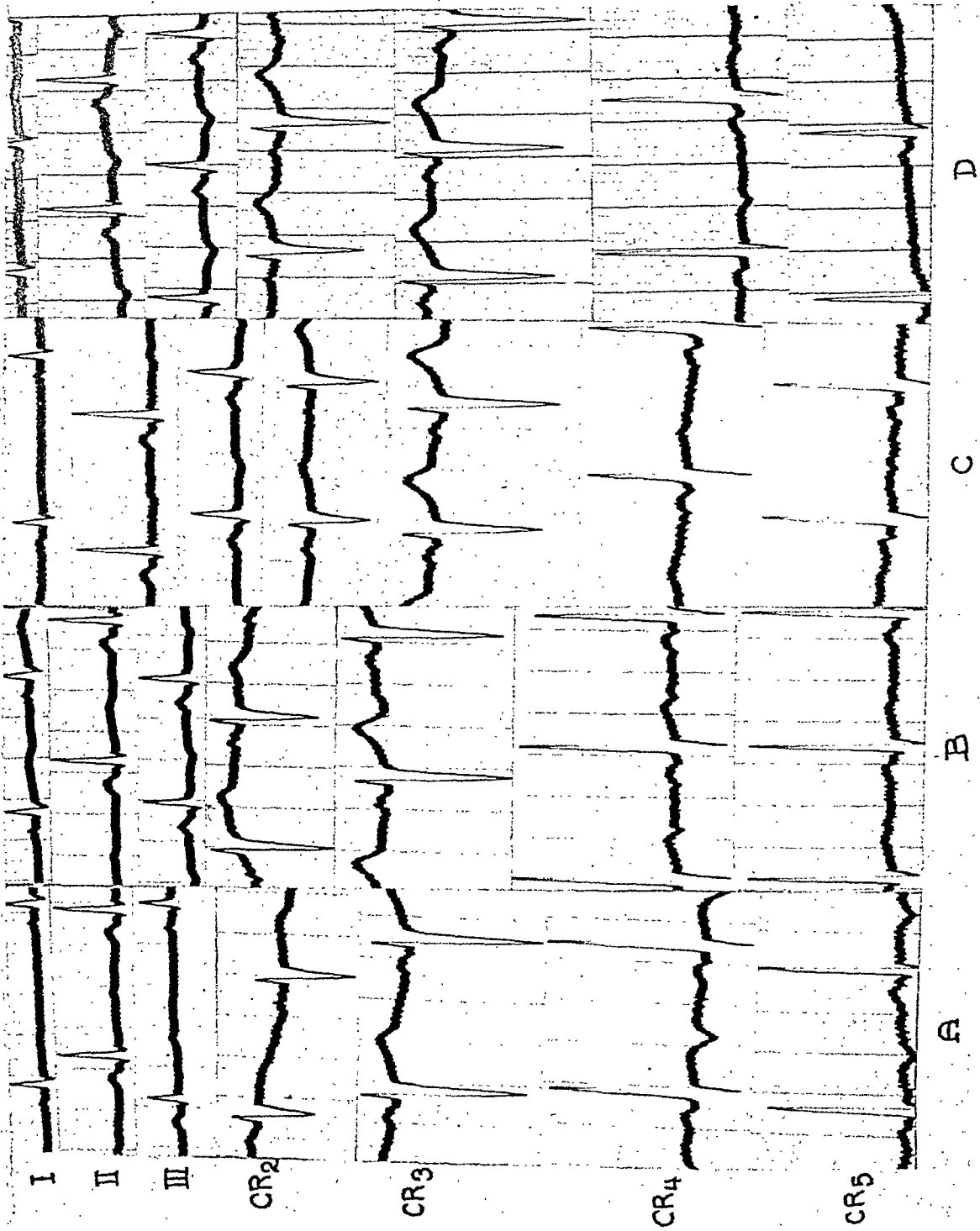
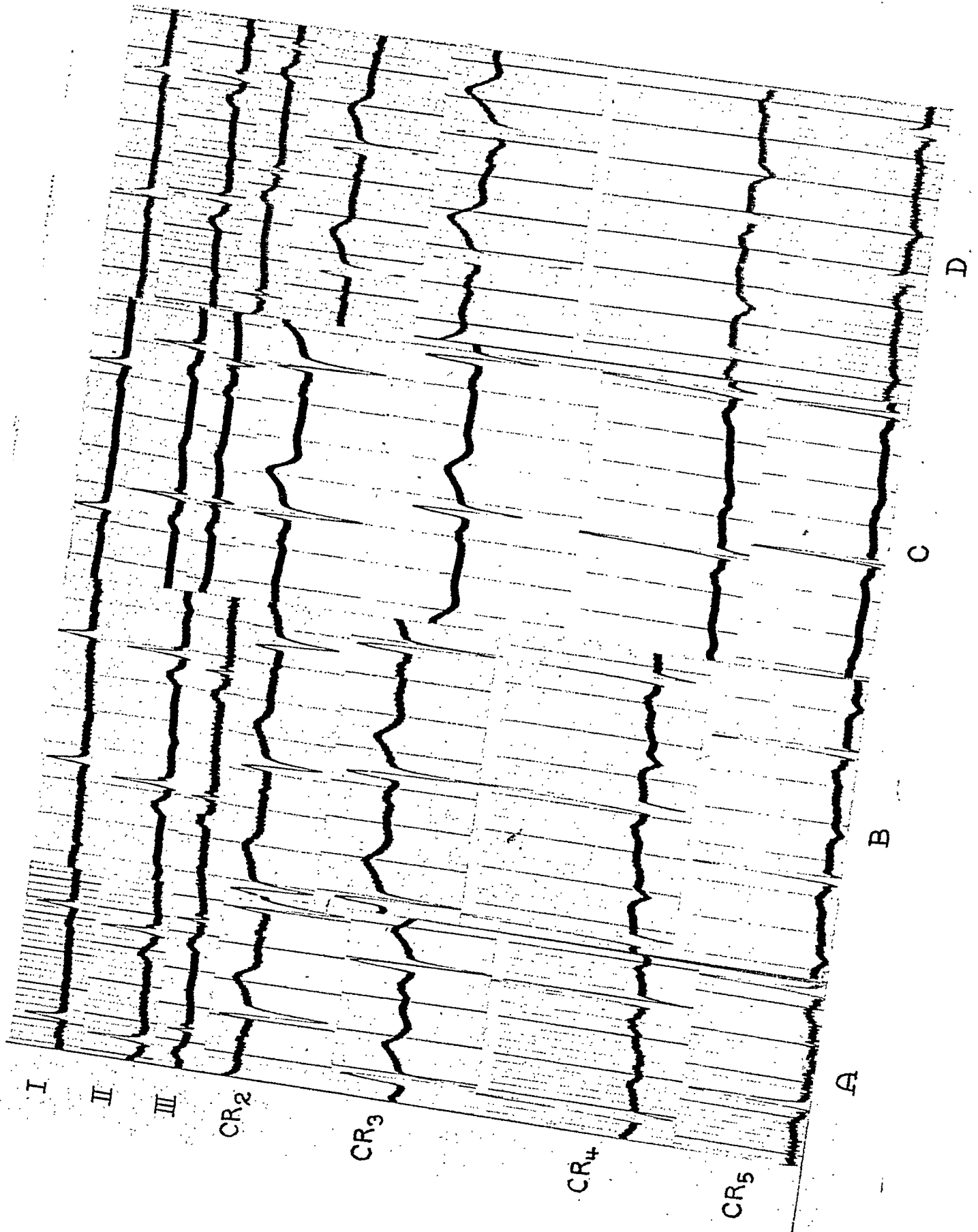


Fig. 3.—Case 11. A, Electrocardiogram of white man, 29 years of age, with seronegative primary syphilis, made June 12, 1946, before treatment, which was started on same day. 80,000 units were given every three hours. B, Tracing made next day, June 13, 1946. C, Electrocardiograms made June 20, 1946, and D, tracing made July 2, 1946. All subsequent tracings up to July 16, 1946, when he left the country, were similar to D.

STEIGER AND EDEIKEN: ECG CHANGES IN EARLY SYPHILIS



Eleven patients (37 per cent) showed evidence of a Herxheimer reaction. A sharp elevation in temperature occurring six to eight hours after the initial intramuscular injection was considered a manifestation of the Herxheimer reaction, if the temperature exceeded 100° F. by mouth. Temperatures were taken every four hours and careful notes were made as to the exaggeration of skin lesions during this period. The results are as follows:

Herxheimer reactions (total)	11 (37 per cent)	
Electrocardiographic abnormalities before treatment	11 (37 per cent)	(not including two questionable)
Electrocardiographic abnormalities after and not before	4 (13 per cent)	
Total cases with electrocardiographic changes	15 (50 per cent)	
11 cases—Herxheimer reactions	5 showed electrocardiographic changes (45 per cent)	
19 cases—No Herxheimer reactions	10 showed electrocardiographic changes (53 per cent)	

30

The difference between 53 per cent showing electrocardiographic changes and no Herxheimer reaction is not significant as compared to 45 per cent of the cases showing electrocardiographic changes and a Herxheimer reaction. There were four cases showing electrocardiographic abnormalities after penicillin when the prepenicillin electrocardiogram was normal. Two of these four cases had clinical Herxheimer reactions.

Age.—The ages of the thirty patients in this study varied from 15 to 47 years. Electrocardiographic abnormalities were distributed throughout without correlation.

Weight.—The subjects varied in weight from 42 kilograms to 165 kilograms; again there was no correlation.

Sex.—Seventeen of the thirty cases were women (57 per cent) and thirteen men (43 per cent). Eight women showed changes as compared to seven men.

Color.—Twenty-four were Negro and six were white; no race difference in the electrocardiographic changes was noted.

Duration of Infection.—

STAGE	CASES	ECG CHANGES
Seronegative primary	2	2
Seropositive primary	2	1
Secondary	15	6
Recurrent lesions*	11	6
	—	—
	30	15

*Includes relapsing and probable reinfections.

It is interesting to note that changes were present in all phases of early infectious syphilis. The abnormalities in the electrocardiogram, if due to syphilis, seem to occur very early in the infection. Since these changes in some cases were of a very short duration, it is entirely possible that other cases had the same changes and were missed entirely.

Amount of Penicillin.—

14 cases—Initial doses	80,000
15 cases—Initial doses	40,000
1 case —Penicillin beeswax oil, initial dose	150,000

Four cases showing changes after treatment and not before

3 cases—Initial doses	40,000
1 case —Initial dose	80,000

Since the majority of the cases which showed T-wave abnormalities had the changes before penicillin was administered, the dose of penicillin would not enter into the development of electrocardiographic changes. Four cases, however, did show electrocardiographic abnormalities after treatment when the prepenicillin examination had been negative. Three of these four were started on 40,000 units and the other on 80,000 units of sodium penicillin. Since 15 (50 per cent) of this series of thirty cases received an initial dose double that of the remainder, and only one receiving the larger dose showed electrocardiographic abnormalities after treatment, additional evidence is lent to the probability that penicillin is not the cause of these changes.

In light of the evidence of a neurotropic spirochete, we immediately were confronted with the possibility that one strain of spirochete may cause these changes. There were four pairs of patients, each of whom, we were reasonably sure, was infected by the same strain. The results are as follows:

Case 7 and Case 22, husband and wife; neither showed changes

Case 8 and Case 9, sisters infected by the same man; Case 8 showed changes and Case 9 was normal

Case 25 and Case 26, husband and wife; husband, Case 25, was normal and Case 26 showed changes

Case 13 and Case 18, husband and wife; husband, Case 18, was questionable and wife, Case 13, was normal

Although these cases were treated in different stages, and it is entirely possible that changes could have been present and missed, it is interesting to note the marked difference in involvement in these cases, probably involving the same spirochete.

Previous Treatment.—All cases were dark-field positive at the time of the initial electrocardiographic examination. Seven cases, however, gave histories of previous antisyphilitic therapy. In no case could we definitely prove a reinfection, so these cases are simply classified as recurrent lesions.

Three individuals (43 per cent) in the seven with a history of previous treatment showed changes. Twelve cases (52 per cent) of the twenty-three who had no previous treatment showed electrocardiographic abnormalities.

Type of Infection.—Twenty-eight of these thirty patients had cerebrospinal fluid examinations. These, however, were done during the first six days of treatment, and none before penicillin was started. Two of the twenty-eight cases showed positive spinal fluids; Case 14 showed a type II fluid, and Case 30 showed a type III. Both of these cases showed definite electrocardiographic changes. Case 29, who had a probable syphilitic nephrosis, showed low amplitude T waves in all leads. These changes, however, were not sufficiently abnormal to be included in the 15 cases showing changes. Case 12 had x-ray and physical evidence of a periostitis, and an initial blood test of 512 Kline units. There were, however, no cardiac changes. No case of ocular or liver involvement was noted in this series.

Controls.—Eight patients showing no historical, physical, or serologic evidence of syphilis were treated with the same amounts of penicillin as the thirty syphilitic patients. These control cases had minor dermatologic diseases such as pyodermas, and so forth, with no evidence of systemic disease. None of these eight showed any electrocardiographic changes during or after the administration of 4.8 million units. This control series is admittedly small. In view of the fact that the majority of the electrocardiographic changes in the syphilitic patients were seen prior to the administration of penicillin, we think this control significant.

CASE REPORTS

CASE 11.—A 29-year-old white man was admitted to the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on June 12, 1946, with the diagnosis of seronegative primary syphilis.

The patient, a merchant seaman, landed in this country June 3, 1946. His last sexual contact was in India some four weeks before, just prior to embarking for the United States. He gave a blood transfusion to a friend the day he landed, and a confirmed blood test on June 3 was negative. On June 4, he noted a small papule near the frenulum. This progressed to an ulcer 1 cm. in diameter by June 11. He had taken no digitalis or other drugs.

The patient was 5 feet, 8½ inches in height and weighed 136 pounds. The blood pressure was 126/80, the oral temperature was 98.6° F., and the pulse 80 per minute. There was a sharply defined ulcer on the glans penis extending to the frenulum and a 1 cm. x 1.5 cm. nonpainful node in the left inguinal region. No other skin or mucous membrane lesions were present. Examination of the heart showed no enlargement, no murmurs, and a regular rhythm. The electrocardiograms are shown in Fig. 4.

The important laboratory data include: a positive dark-field examination of material from penile lesion on June 11, 1946; negative Kline, Kolmer, Mazzini, and Kahn tests on June 11, 1946; negative Kolmer, Kline, and Mazzini tests again in July, 1946; and a cerebrospinal fluid examination, June 19, 1946, which showed 2 cells, Wassermann 0000, protein 30 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin; six hours later he had a chill and then a temperature of 102° F. by mouth. His pulse was 118 per minute at the height of fever, but on the following day when his temperature had fallen to 101°, his pulse was 130. By the third day both pulse and temperature had leveled off and remained normal throughout the hospital stay. He received 120 injections of 80,000 units each between June 12 and June 27, 1946. At no time did he complain of cardiac symptoms.

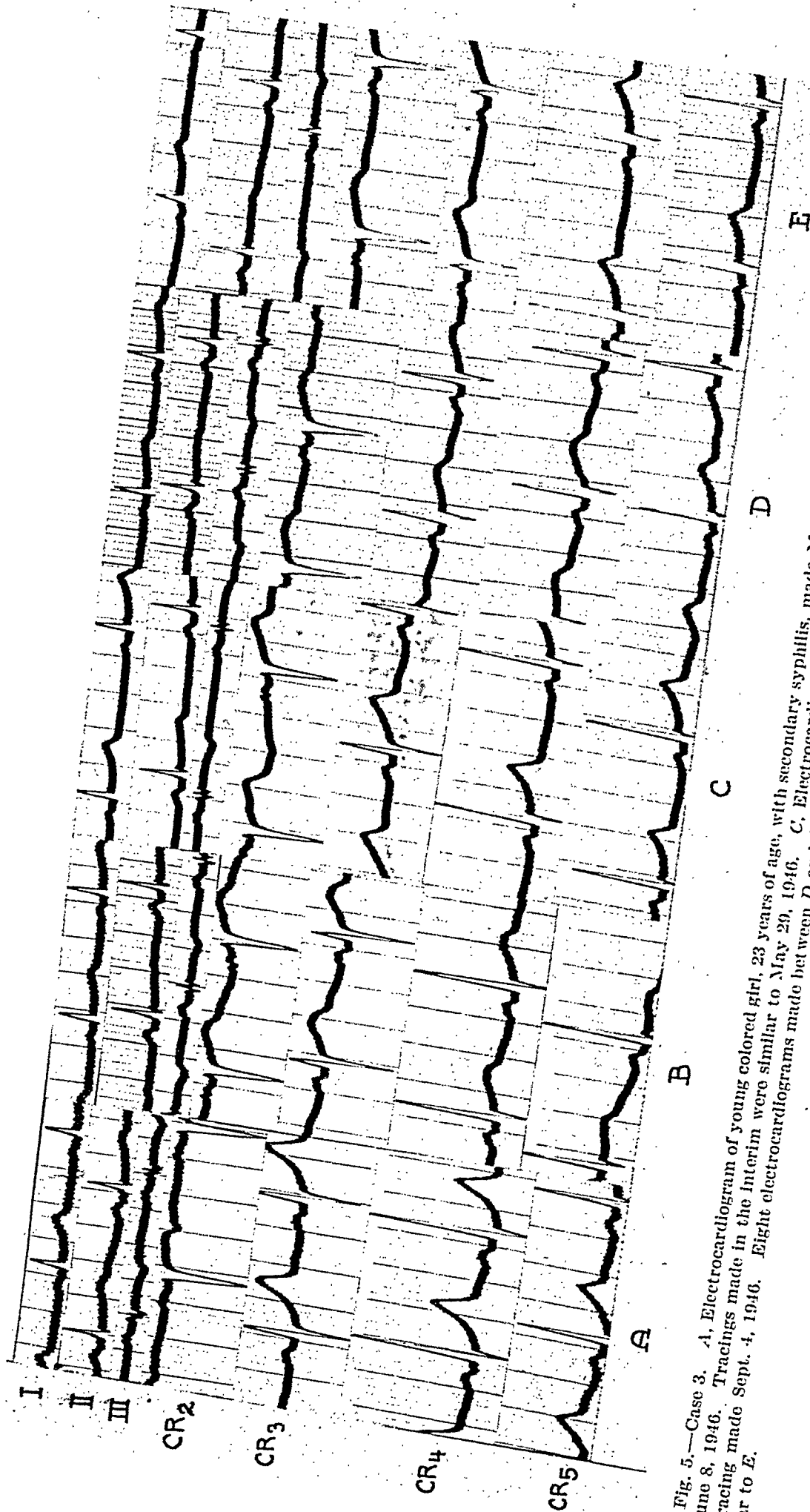


Fig. 5.—Case 3. A, Electrocardiogram of young colored girl, 23 years of age, with secondary syphilis, made May 29, 1946, before 'treatment'. B, Tracing made on June 8, 1946. Tracings made in the interim were similar to May 29, 1946. C, Electrocardiogram made June 11, 1946, and D, one month later, July 11, 1946, similar to E. Eight electrocardiograms made between D and E showed fleeting changes, but tracings made Oct. 1, 1946, and Nov. 6, 1946, were

CASE 3.—A colored woman, 23 years of age, was admitted to the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on May 29, 1945, with a diagnosis of secondary syphilis.

The patient had negative serologic tests for syphilis in 1939 and in 1942, and gave no history of previous antisyphilitic treatment. A small lesion on the labia was noted two months before admission. This cleared spontaneously, but one month later numerous lesions appeared over the entire vulva and trunk. There was no history of digitalis or other drug ingestion.

The patient was 5 feet, 2 inches in height and weighed 118 pounds. Her oral temperature was 98° F., respiration, 20, pulse, 72 per minute, and blood pressure, 118/70. There were resolving hyperpigmented papules over the trunk, macules of the palms and soles, and condylomatous lesions of the genitalia and perineum. The throat was inflamed and her voice was slightly husky. The heart was normal in size and the sounds were of good quality, no murmurs were heard. The electrocardiograms are shown in Fig. 5.

The important laboratory data were as follows: dark field from condylomata positive for *Treponema pallidum* on May 29, 1946; Kolmer positive, Mazzini positive, Kline 256 units on May 29, 1946; a cerebrospinal fluid examination on June 5, 1946, showed 1 cell, Wassermann 0000, protein 10 mg., and mastic 0000000000.

The patient received the first injection of 80,000 units of sodium penicillin on May 29, 1946, and this was continued every three hours for 120 injections. She completed the 9.6 million units on June 18, 1946, without nausea, cardiac symptoms, urinary difficulties, or pain. There was no Herxheimer reaction as far as temperature, pulse, or skin were concerned.

CASE 14.—A 47-year-old colored man was admitted to the medical ward of the Hospital of the University of Pennsylvania on July 24, 1946, for observation of abdominal pain and vomiting of four weeks' duration. A penile lesion of approximately six weeks' duration was discovered along with a follicular eruption of approximately three weeks' duration. There was a history of annual negative blood tests since 1940.

On physical examination he was 5 feet, 8½ inches in height, weighed 126½ pounds, and his oral temperature was 99° Fahrenheit. His respiration was 18, pulse, 82 per minute, and blood pressure, 130/80. The patient was emaciated and vomited frequently. There was a follicular eruption on the arms and macules on the palms and soles. The urethra was indurated and small indurated ulceration could be seen at the meatus. The deep reflexes and pupillary reflexes were normal. There was generalized lymphadenopathy and the liver was enlarged 2 cm. below the costal margin. Roentgen study of the gastrointestinal tract disclosed gastric retention with spasm and deformity of the antrum. A gastroscopy performed Aug. 6, 1946, disclosed an ulcer of pyloric antrum with scarring of lesser curvature. The cardiac findings were negative and there was no history of digitalis or other drug ingestion. The electrocardiograms are shown in Fig. 4.

The important laboratory data were as follows: dark field from meatus positive for *Treponema pallidum* on July 31, 1946; Kolmer and Mazzini strongly positive, Kline 256 units on July 31, 1946; and a cerebrospinal fluid examination on July 29, 1946, which showed no cells, Wassermann slightly positive, protein 60 mg., and colloidal gold 0111000000.

The patient was started on 40,000 units of sodium penicillin on July 31, 1946. There was no febrile or clinical Herxheimer reaction. Thirty-six hours after the start of the penicillin, however, all nausea and vomiting ceased and the course was uneventful. Because of the gastric lesion in a man of 47 years, he was operated upon and the nonspecific ulcer was found. He did not complain of cardiac symptoms before or after operation.

CASE 19.—A 37-year-old white man entered the Institute for the Study of Venereal Disease of the Hospital of the University of Pennsylvania on April 15, 1946, as contact of his bride of three months, who had florid secondary syphilis. He was clinically and serologically negative at the time, but returned two weeks later, May 2, 1946, with a large, indurated, dark-field positive penile lesion. There was no history of digitalis or other drug ingestion.

The patient was 5 feet, 8 inches in height, and weighed 151 pounds. His temperature was 98.2° F., his pulse, 72 per minute, and blood pressure, 122/78.

On his first admission, May 2 to May 19, 1946, there was an indurated ulcer on the corona, satellite lymphadenopathy in the right inguinal region, but no generalized lymph node enlarge-

ment. There were no other skin or mucous membrane lesions. Examination of the cardiovascular system was entirely normal except for the electrocardiogram; he had no cardiac complaints. The electrocardiograms are shown in Fig. 2.

The important laboratory data were as follows: Dark-field positive penile lesion on May 2, 1946; Kolmer and Eagle strongly positive, and Kline 64 units on May 2, 1946; and a cerebral spinal fluid examination on May 8, 1946, which showed 1 cell, Wassermann 0000, protein 20 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin on May 4, 1946, and received 120 such injections intramuscularly at three-hour intervals (total, 9.6 million units). The lesion was completely healed and all induration gone on June 21, 1946. Blood tests showed: Kolmer strongly positive, Kline 64 units on June 3, 1946; and Kolmer doubtful, Kline less than one unit on June 21, 1946.

His second admission was from July 31 to Aug. 15, 1946. A lesion had appeared one week before at the same site as the previous one. There were solitary nodes in the right inguinal region, but no other skin or mucous membrane lesions were present. Examination of the heart revealed no changes compared to May 19, 1946, except that the electrocardiogram was normal.

The important laboratory data were as follows: dark field from penile lesion positive for *Treponema pallidum* on July 31, 1946; Kolmer strongly positive, Kline 256 units on July 31, 1946; and a cerebral spinal fluid examination on Aug. 2, 1946, which showed 1 cell, Wassermann 0000, protein 20 mg., and mastic 0000000000.

The patient was started on 80,000 units of sodium penicillin on July 31, 1946, and received 120 injections at three-hour intervals for a total of 9.6 million units. Again the lesion completely epithelialized by the end of treatment. He had a moderate postspinal headache which disappeared in forty-eight hours. On the thirteenth hospital day, he developed typical giant urticaria which was relieved by Benadryl. The penicillin therapy was not interrupted. The patient was seen on Sept. 12, 1946, at which time he showed no clinical evidence of syphilis, his chancre site being nonindurated, Kolmer positive, and Kline 32 units.

His third admission was from Oct. 4, 1946, to Oct. 20, 1946. The lesions reappeared eight days before admission (Sept. 26, 1946) at the same site as the previous ones, and had the same general configuration as the previous ones. General examination was essentially negative except for two discrete lymph nodes in the right inguinal region. Examination of the heart showed no changes compared to Aug. 31, 1946; the electrocardiogram was normal.

Important laboratory data were as follows: Darkfield from penile lesion was positive for *Treponema pallidum* on Oct. 4, 1946; Kolmer and Mazzini were strongly positive, Kline 256 units on Oct. 4, 1946; and a cerebral spinal fluid examination on Oct. 9, 1946, showing 1 cell, Wassermann 0000, protein 10 mg., and mastic 0000000000.

The patient was started on sodium penicillin, 80,000 units every three hours for 120 doses. No febrile or clinical Herxheimer reaction was present and no evidence of urticaria or pruritus was noted.

This patient's only admitted contact, his wife, was followed during this siege of relapses and had been seropositive without lesions until Oct. 6, 1946, when she developed dark-field positive secondaries and was admitted for study.

DISCUSSION

It is well known that factors other than actual heart disease, such as drugs, change in position from recumbent to sitting or standing, autonomic nerve influences, and changes in the constitution of the blood, for example, hyperventilation, may produce changes in the T waves of the electrocardiogram. Even trivial influences such as smoking, or drinking cold liquids, or even mild exertion may also cause changes in the T waves. To the best of our knowledge, however, these factors were not operative on our cases. Studies of large series of normal young individuals have shown T-wave and RS-T segment changes to occur in a

small percentage of cases. In Ferguson and O'Connell's¹⁴ series of 1,812 midshipman who were clinically normal, eight showed T waves in Lead II which were negative, isoelectric, or diphasic; but in no case was the T wave in Lead I negative or diphasic. In 299 unselected college students, of whom 295 were clinically negative, studied by Wood, Wolferth, and Miller,¹⁵ elevation of the RS-T segment was noted in eighteen and the T wave in Lead II was partly inverted in four, but in no case was the T wave in Lead I inverted. In sixteen instances, however, the height of the T wave in Leads I and II or both, was 1 mm. or less. In Graybiel, McFarland, Gates, and Webster's¹⁶ series of 1000 young men, the RS-T segment was occasionally elevated more than 1 mm., but was rarely displaced downward. The T wave in Lead II was inverted in two instances, and in one case it was diphasic; in Lead I, the T wave was sometimes low, but in no instance was it inverted. These studies emphasize that RS-T segment and T-wave changes occur in supposedly normal young individuals, but also emphasize their rarity. In the older age groups, Wood, Wolferth, and Miller¹⁵ studied 229 corporation executives, a large majority of whom were older than 40 years. In this group abnormal electrocardiograms were found in sixteen and questionable findings were present in 107 others. In the former, however, which included T waves inverted or partly inverted in Leads I and II, all had cardiovascular disease or were known to have suffered from it subsequently, except two who were not followed. It follows, therefore, that while the T wave in Lead II may occasionally be inverted or diphasic in the electrocardiogram of supposedly normal individuals, an inverted or diphasic T wave in Lead I is rarely observed except in the presence of a cardiovascular abnormality.

In all our cases, electrocardiograms were made at frequent intervals, and although too much importance might not be attached to certain changes in the T wave or RS-T segment in individual tracings, the fact that they varied in different electrocardiograms of the same individual taken at frequent intervals, and sometimes in different leads, would indicate that the changes were significant. Slight changes in the amplitude of T waves were not considered significant and these cases are not included in the abnormal group. In one case (Fig. 2.), however, the initial electrocardiogram was considered doubtful, but the gradual improvement in the T waves over a period of eleven days while under treatment indicated that the slight T-wave changes were abnormal for this individual. Although none of the 3,107 subjects included in the three large groups of supposedly normal young individuals showed inversion of the T wave in Lead I, three (20 per cent) of the fifteen cases considered abnormal in this study showed inverted T waves in Lead I in at least one of the electrocardiograms. Furthermore, the large percentage of patients (50 per cent) who showed changes in the electrocardiogram, either before or during treatment, suggests that the abnormalities observed in the electrocardiogram could not be due to extracardiac factors, although in no instance were there any complaints referable to the cardiovascular system. In the absence of autopsy material and because there is such marked difference of opinion (Boyd,⁵ and Warthin⁹) as to changes which occur in the heart muscle in early syphilis, one can only spec-

ulate as to the possible causes of the electrocardiographic abnormalities. Several possibilities present themselves:

1. That they are due to a toxic action of penicillin, such as that which has been attributed to arsenic, sulfonamides, and other drugs.
2. That the changes are due to a toxemia without actual cardiac involvement, such as occurs in some infectious diseases.
3. That the abnormalities are due to a disturbance in the heart muscle either because of direct action of the spirochetes within the heart muscle or intercellular spaces or by their destruction by penicillin.

We believe the first possibility can be dismissed because: (1) In eleven cases T-wave or RS-T segment changes were present before treatment with penicillin or before other forms of treatment were initiated. (2) In our experience comparable changes were not present in penicillin-treated infections due to other causes. (3) In a small control series, eight subjects, there was no instance of electrocardiographic change while penicillin was being used. Although small, this control group is considered significant since the majority of changes that developed in the abnormal group occurred before treatment.

The suggestion that the electrocardiographic changes may be of toxic origin seems to be refuted by the fact that there was no clinical, urinary, or hematologic evidence of toxemia except during a short period (usually six to twelve hours after treatment was started) when a sharp rise in temperature of Herxheimer type occurred in one-third of the cases. However, in most cases the electrocardiograms showed changes while the patient was apparently well and after treatment was completed, and there was no correlation between Herxheimer reactions and electrocardiographic changes. Young¹⁷ recently reported thirteen cases with electrocardiographic changes as the result of upper respiratory infections. As in our cases, changes frequently occurred while the patient was apparently well, but he states that in the few cases reported in the literature where sudden death occurred during acute tonsillitis, a diffuse widespread myocarditis was found at autopsy. In the absence of autopsy material, however, one cannot state categorically that the changes in our group of cases are not of toxic origin.

In our opinion the possibility that the electrocardiographic abnormalities are due to changes within the heart muscle seems most tenable. As stated previously, however, the lack of autopsy material and the marked difference in the opinion of pathologists as to the cardiac changes in early syphilis, makes this suggestion a very fertile field for speculation.

CONCLUSIONS

1. Thirty cases of early infectious syphilis were studied and fifteen showed definite electrocardiographic changes, but in no instance were there cardiac complaints.
2. The electrocardiographic abnormalities consist of T-wave and RS-T segment changes in limb and/or chest leads.

3. There is no correlation between the febrile Herxheimer reaction and the incidence of these electrocardiographic changes.

4. The electrocardiographic abnormalities occur in all stages of early infectious syphilis.

5. Penicillin does not appear to be responsible for these electrocardiographic changes.

6. In some instances the changes are transient, but in others they may last for several months; it is not possible to state at this time whether the changes may be permanent.

Special acknowledgment is made of the valuable aid of Charles C. Wolferth, M.D., Director of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, whose departmental facilities and direction were made available for this work; and of the helpful suggestions and criticisms of Dr. John H. Stokes.

REFERENCES

1. Arnett, J. H.: Cardiovascular Findings in Women With Syphilis, *Am. J. M. Sc.* 176:65, 1928.
2. Wilson, F. W., Wile, W. J., Wishart, S. W., and Herrmann, G. R.: Changes in the EKG Following Arsphenamine Treatment of Cardiac and Aortic Syphilis, *Proc. Soc. Exper. Biol. & Med.* 23:275, 1926.
3. Chamberlain, E. W., and Follows, J. H.: The EKG in Syphilis. An Examination of 232 Cases of Syphilis and 156 Controls, *Quart. J. Med.* 26:221, 1933.
4. Martland, H. S.: Syphilis of the Aorta and Heart, *AM. HEART J.* 6:1, 1930.
5. Boyd, W.: A Text-Book of Pathology: An Introduction to Medicine, Philadelphia, 1943, Lea & Febiger, p. 365.
6. Turner, K. B., and White, P. D.: The Heart and the Aorta in Early Syphilis, *Arch. Int. Med.* 39:1, 1927.
7. Grassmann, K.: Klinische Untersuchungen an den Kreislaufs-organen in Frühstadium der Syphilis, *Deutsches Arch. f. klin. Med.* 68:455, 1900.
8. Warthin, A. S.: Primary Tissue Lesions of the Heart Produced by *Spirochaeta Pallida*; Trans. XVII, Internat. Congress Med., Sec. Path. Part II, 299, 1913.
9. Ibid: Primary Tissue Lesions in the Heart Produced by *Spirochete Pallida*, *Am. J. M. Sc.* 140:7, 1914.
10. Sadusk, J. F.: Discussion of Papers by Leifer, Chargin, and Hyman, and Elliott, Baer, Shaffer, Usher, and Lough, *J. A. M. A.* 117:1165, 1941.
11. Geiger, A. J., Craig, B., and Sadusk, J. F.: Observations in the Massive Dose Arsenotherapy of Early Syphilis by the Drip Method II. Electrocardiographic Abnormalities Associated With Massive Arsenotherapy, *Yale J. Biol. & Med.* 14:357, 1942.
12. Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology, Philadelphia, 1945, W. B. Saunders Company.
13. Klotz, S. D., and Crede, R. H.: Electrocardiographic Changes in Early Syphilis Prior to and Upon Completion of Intensive Arsenotherapy, *AM. HEART J.* 30:551, 1945.
14. Ferguson, D., and O'Connell, J. T.: Cardiovascular Observations, *U. S. Nav. M. Bull.* 24:860, 1926.
15. Wood, F. C., Wolferth, C. C., and Miller, T. G.: Electrocardiography in War Medicine, *War Med.* 1:696, 1941.
16. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1000 Young Healthy Aviators, *AM. HEART J.* 27:524, 1944.
17. Young, D.: Electrocardiographic Changes Occurring During Upper Respiratory Infections, *AM. HEART J.* 32:303, 1946.

COMPARATIVE STUDY OF POTASSIUM THIOCYANATE AND OTHER DRUGS IN THE TREATMENT OF ESSENTIAL HYPERTENSION

ARTHUR RUSKIN, M.D., AND W. FRANK MCKINLEY, M.D.*
GALVESTON, TEXAS

HUNDREDS of drugs have been and are being used in the therapy of essential hypertension, frequently without critical analysis of their value in either abolishing symptoms or lowering the systolic and diastolic blood pressure. Ayman^{1,2} has pointed out the enormous variabilities of blood pressure under various conditions with or without therapy. He noted variations in systolic pressure up to 40 to 100 mm. of mercury. Every practitioner has seen hypertension of over 220/120 interspersed with long periods of normal blood pressure without therapy of any kind. Claims of symptomatic relief from headaches, dizziness, and other symptoms of essential hypertension by various methods of therapy have been countered by noted relief from symptoms in 82 per cent of the cases following administration of dilute hydrochloric acid in placebo dosage.³

More recently, Kapernick⁴ studied the effect of several reputedly hypotensive drugs, including xanthine derivatives, phenobarbital, erythrol tetranitrate, and representatives of the mistletoe and garlic groups, with negative results. However, the various drugs were tried in different small groups of cases, and potassium thiocyanate was not among them. In the comparative study of Evans and Loughnan⁵ numerous therapeutic methods, including potassium thiocyanate, were tested in similar fashion and found wanting. In general, symptomatic relief was as common, and significant drops in blood pressure as infrequent, in the placebo as in the other groups. Potassium thiocyanate apparently caused actual increases in symptoms and blood pressure in a minority of cases.

Since the introduction of blood level checks in thiocyanate therapy by Barker⁶ in 1936, twenty-one favorable and five unfavorable reports on its efficacy in human hypertension have been listed.⁷ The same reviewer stated, however, that "none of the clinical reports have completely eliminated all the variables which might cause unrelated blood pressure variation." Barker and associates⁸ have now treated some hundreds of patients for years, with favorable effects in some half to three-quarters of their cases. Their criteria of falls of systolic pressure, 30 to 60 mm., and of diastolic 20 to 40 mm., would seem adequate except for lack of adequate controls and questionable methods of measuring the changes in blood pressure, as criticized later in this discussion. Provided

*From the University of Texas Medical School, and the Heart Station of the John Sealy Hospital, Galveston.

Received for publication Feb, 24, 1947.

the blood level of potassium thiocyanate was kept at 8 to 12 mg. per cent, serious or fatal toxic reactions were avoided.

Nevertheless, the Council of Therapy of the American Medical Association has failed to endorse this mode of therapy on the grounds of incomplete proof of its efficacy in human essential hypertension, its toxic effects, and its failure to lower the blood pressure in experimental hypertensive animals except at toxic blood levels.⁹ The pharmacologic mode of action of the thiocyanates is also far from clear, although numerous theories have been proposed.⁷ While one group of investigators¹⁰ has claimed that normal (pretreatment) serum thiocyanate is inversely proportional to the blood pressure, thereby providing a rational support for its therapeutic use in hypertension, others¹¹ have been unable to confirm this.

A restudy of the preceding claims, with adequate controls, was begun by us in 1942. Since then, six drugs, unknown to the patients, have been administered in various rotations to sixty-eight clinic patients with uncomplicated essential hypertension. The dosages were as follows: phenobarbital, 32.0 mg. three times daily; glucophylline (methyl-xanthine derivative), 0.3 Gm. three times daily; mannitol hexanitrate, 65.0 mg. three times daily; niacin, 50.0 mg. three times daily; and a placebo (lactose or sodium bicarbonate), 0.3 Gm. three times daily. Periods of therapy were interspersed with rest or control intervals of two to four weeks. Potassium thiocyanate was started at 0.2 Gm. three times a day after three blood serum levels were obtained in the fasting state and following a tobacco-free interval of three or more days, as recommended.¹¹ Serum potassium thiocyanate concentration was determined by a method adapted to the Evelyn colorimeter.¹² In many cases, weekly blood levels reached 20 mg. per cent (to evaluate the drug more thoroughly), and, at times, inadvertently, higher levels. Maintenance dosages of potassium thiocyanate necessary to maintain therapeutic blood levels varied from 0.2 to 1.2 Gm. daily, and the drug was continued for three months, as recommended for proper evaluation.⁸ The rest interval after thiocyanate therapy was at least a month, or long enough for return to the pretreatment blood level.

Blood pressures were recorded twice weekly between 9 and 10 A.M., in the same arm, by the same observer, and to the nearest 5 mm. of three readings, recording both the fourth and the fifth phases whenever possible.¹³ Constant conditions of preliminary rest and medication were observed.

RESULTS

It was found that two kinds of estimates of the effect of the various drugs upon the blood pressure checked closely and disagreed markedly with the usual method of contrasting the blood pressure just before and following the therapeutic agent. One was to compare the range of systolic and diastolic pressures during the control and therapeutic periods. The other was to contrast the medians of the numerous blood pressure readings during medicinal and drugless periods. When, as happened infrequently, the two computations disagreed by 5 mm., the figure closer to the one obtained by the before-and-after method was

taken as the correct result. It cannot be too strongly emphasized, however, that results obtained from the graphed blood pressures before and during drug administration (Fig. 2), depending as they do upon the fallacy of taking a variable (the pretreatment blood pressure) for a constant, are probably worthless, even for comparative purposes.

The weighted results of the effects of the six drugs upon the systolic and diastolic blood pressures are charted in Fig. 1 and Table I. It will be seen that while potassium thiocyanate was associated, especially in isolated instances, with more marked drops in systolic and in diastolic pressures than the other

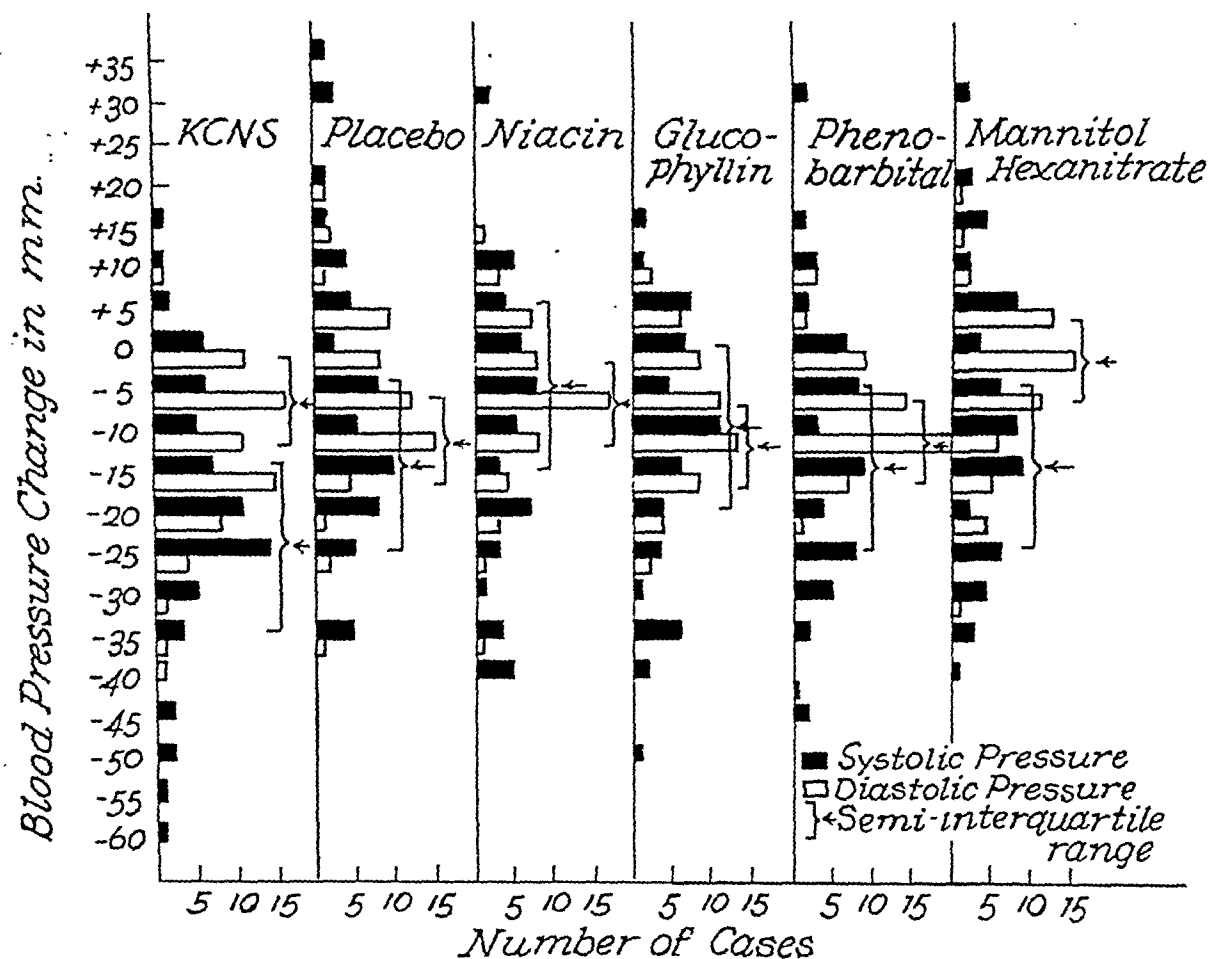


Fig. 1.—Effects of the six drugs upon the systolic and diastolic blood pressures, as finally obtained from range-to-range and median-to-median comparisons of the control and therapeutic periods. Minus signs indicate falls; plus signs, rises in pressure.

drugs, tremendous overlapping was present. Mild to moderate drops in blood pressure were frequent following the exhibition of all six drugs, as had been noted previously with and even without various modes of therapy.² In a small minority, no changes and even actual rises in blood pressure occurred during thiocyanate therapy. This undoubtedly occurred more frequently following the use of the other drugs.

Statistical analysis, for which we are indebted to Dr. J. A. Scott,* revealed somewhat unexpected differences between the results of administration of po-

*Professor of Epidemiology and Statistics.

tassium thiocyanate and the other drugs. The critical ratio of the difference between the means of potassium thiocyanate and placebo in regard to their effects upon the systolic blood pressure was 3.6, and diastolic pressure, 3.5; or the probability of the correctness of the assumption that there was no difference in the two series of results, or that it was due to chance, was less than one in one thousand. On the other hand, the critical ratio of glucophylline and placebo, for example, was 1.3 for the systolic and 1.16 for the diastolic pressure results; or a probability of chance differences of forty in one hundred.

TABLE I. FIGURES OF AVERAGE AND MEDIAN FALLS IN PRESSURE FOLLOWING THE SIX DRUGS, OBTAINED AS DESCRIBED IN FIG. 1 AND IN TEXT

	LOWERING OF BLOOD PRESSURE BY VARIOUS DRUGS			
	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
	AVERAGE	MEDIAN	AVERAGE	MEDIAN
1. Potassium thiocyanate	19.5 mm.	25 \pm 10 mm.*	10.6 mm.	5 \pm 5 mm.
2. Placebo	9.4	15 \pm 10	5.4	10 \pm 5
3. Niacin	11.1	5 \pm 10	4.9	5 \pm 5
4. Glucophyllin	12.8	10 \pm 10	7.0	10 \pm 5
5. Phenobarbital	12.8	15 \pm 10	7.1	10 \pm 5
6. Mannitol hexanitrate	8.1	15 \pm 10	3.8	0 \pm 5

*Semi-interquartile range.

A more familiar graphing of results of thiocyanate therapy is seen in Fig. 2, which demonstrates the generally more marked effect of potassium thiocyanate in lowering the systolic rather than the diastolic blood pressure. Fig. 2 also shows that there is no consistent relation between the levels of potassium thiocyanate and the blood pressures during therapy. Nevertheless, in those patients in whom serum thiocyanate exceeded 15 mg. per cent, diastolic pressures fell over 10 mm. twice as often as they failed to be lowered; whereas, in those with serum levels below 15 mg. per cent, diastolic pressure depressions failed to occur in the majority of cases (Table II).

TABLE II. BLOOD PRESSURE DEPRESSION AND THERAPEUTIC SERUM POTASSIUM THIOCYANATE LEVEL IN SIXTY-EIGHT CASES

SERUM POTASSIUM THIOCYANATE	S. P. FALL 20 MM. PLUS	S. P. FALL <20 MM.	D. P. FALL 10 MM. PLUS	D. P. FALL <10 MM.
Over 15 mg. per cent	26	15	27	14
Under 15 mg. per cent	17	10	11	16

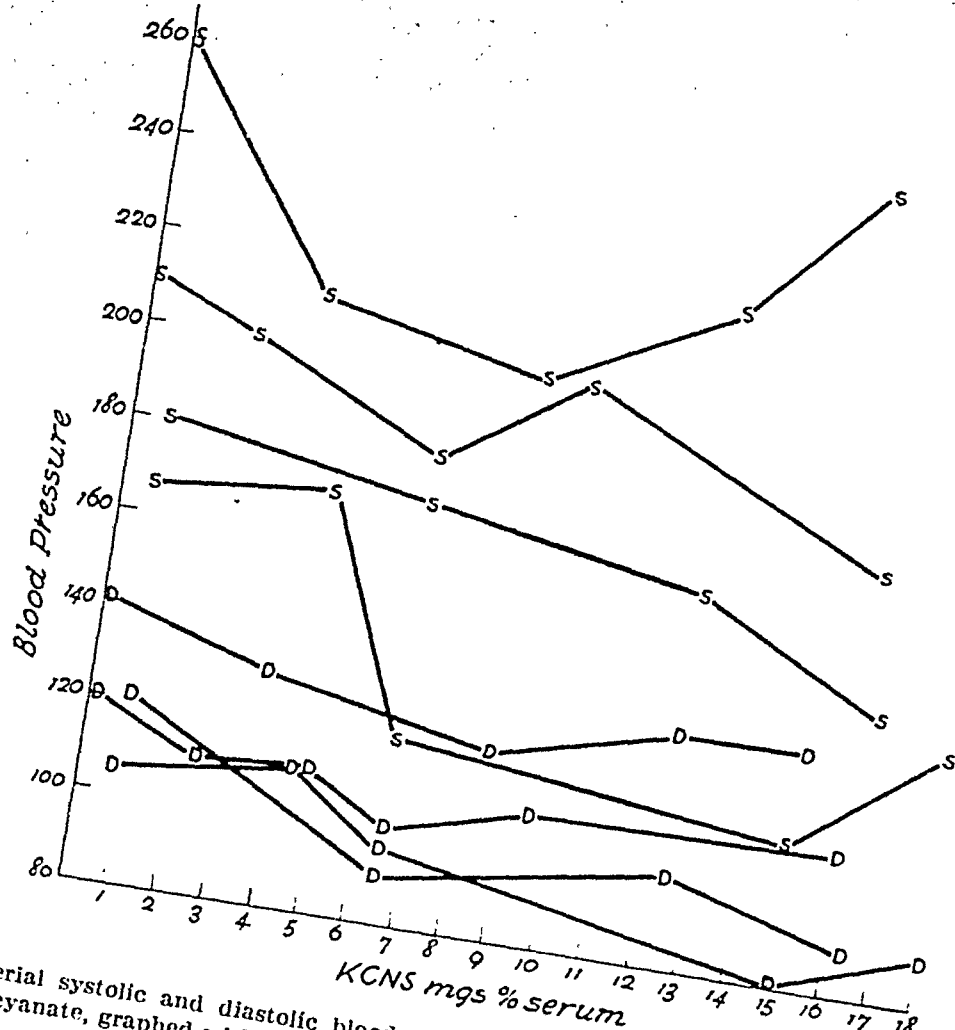


Fig. 2.—Serial systolic and diastolic blood pressures in four representative cases treated with potassium thiocyanate, graphed with regard to the level of serum thiocyanate, but not all in temporal sequence.

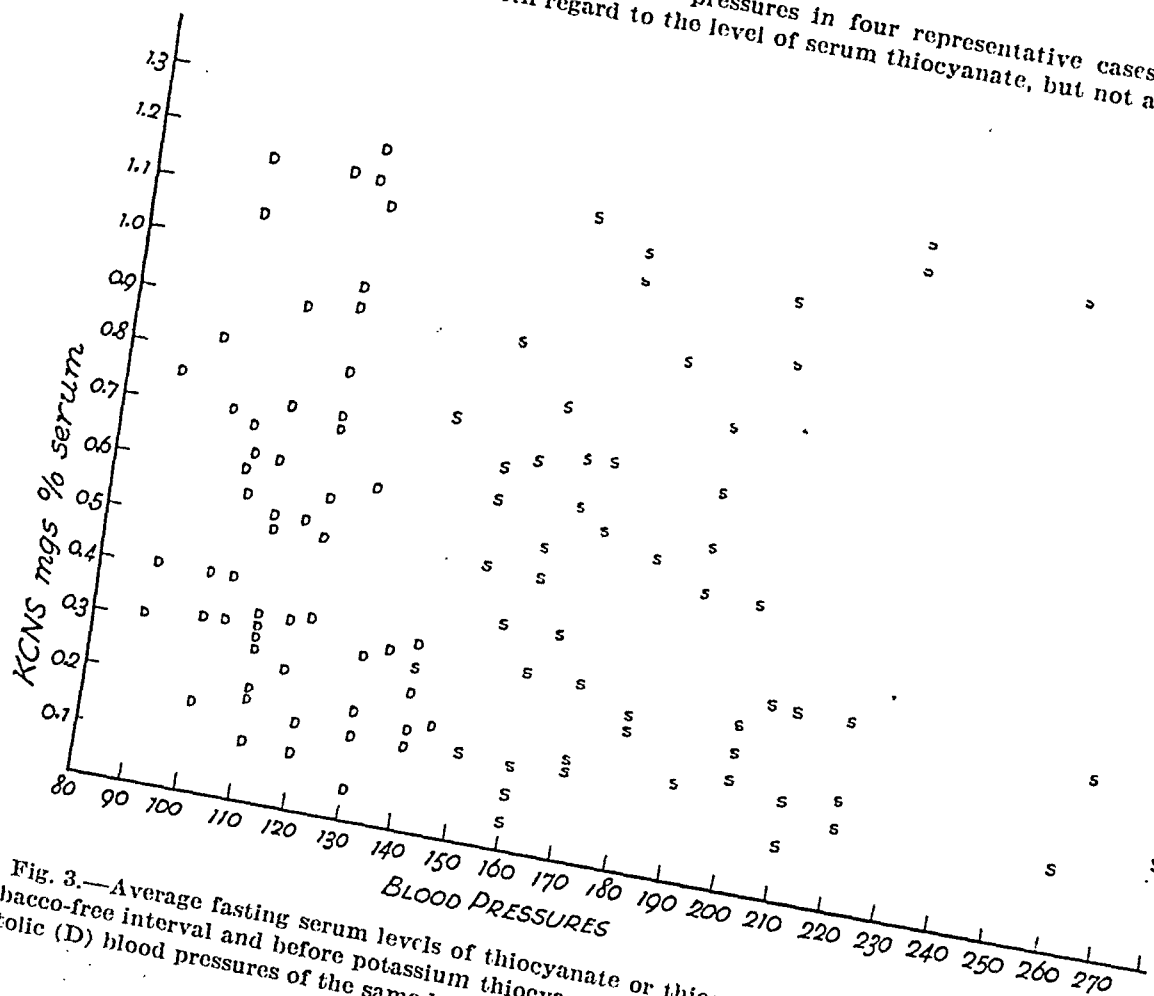


Fig. 3.—Average fasting serum levels of thiocyanate or thiocyanate-like substance obtained after a tobacco-free interval and before potassium thiocyanate therapy, plotted against the systolic (S) and diastolic (D) blood pressures of the same hypertensive patients.

A general lack of correlation between the systolic and diastolic blood pressures of hypertensive patients and the resting levels of serum thiocyanate is seen in Fig. 3. This contradicts the results of Caviness and associates.¹⁰ A similar lack of correlation is demonstrable for normotensive individuals (fifty cases, not shown). It is to be admitted that the method is inexact for such small amounts of thiocyanate or thiocyanate-like substance as are present in normal and hypertensive sera. While the resting serum levels varied from 0 to 1.93 mg. per cent, variations up to 50 per cent in successive determinations in the same individuals were not uncommon, particularly for very low levels.

Relief of symptoms was greatest in the groups receiving the placebo and niacin, and least in the group receiving potassium thiocyanate (Table III). The incidence of actual increase in symptoms was about equal in all groups except the group receiving thiocyanate, which presented the most marked additional complaints. Not unexpected were the occasional dizziness in the hexanitrate-treated patients, and sleepiness or loss of libido in the phenobarbital-treated group. The presumable toxic effects of potassium thiocyanate are listed in Table IV. The most common were dizziness, fatigability and weakness, headache, and nausea. In cases in which serum thiocyanate reached over 15 mg. per cent, symptoms occurred or were intensified in thirty of forty-two cases; in those in which serum thiocyanate remained below 15 mg. per cent, symptoms occurred or were intensified in only thirteen of twenty-six cases.

TABLE III. EFFECTS OF VARIOUS DRUGS ON SYMPTOMS IN SIXTY-EIGHT HYPERTENSIVE PATIENTS

	INCREASE	SAME	DECREASE
Potassium thiocyanate	32	17	19
Placebo	12	5	51
Niacin	12	8	48
Glycophylline	15	10	38
Phenobarbital	15	16	37
Mannitol hexanitrate	20	11	37

TABLE IV. POSSIBLE TOXIC EFFECTS OF POTASSIUM THIOCYANATE IN SIXTY-EIGHT HYPERTENSIVE PATIENTS

Dizziness	26	Blurred vision	2
Weakness	19	Tinnitus	2
Headache	17	Psychosis	2
Nausea	15	Anorexia	2
Malaise, aches	9	Vomiting	2
Nervousness	8	Pruritus	2
Dyspnea	7	Urticaria	2
Palpitation	7	Edema of face	2
Precordial pain	7	Thyroid enlargement	2
Epigastric distress	7	Conjunctivitis	1
Gaseous distention	5	Polyphagia	1
Sleepiness	5	Paresthesias	1
Insomnia	3	Petechial rash	1
Syncope	3	Maculopapular rash	1

In one case, the drug had to be discontinued because of a generalized scaling papular rash, with a serum thiocyanate level of only 4.3 mg. per cent. In another, a psychotic state preceded by a few weeks a rather acute onset of fatal uremia, left ventricular failure, and lobar pneumonia in a 65-year-old Negro, with serum thiocyanate reaching 21.4 mg. per cent before discontinuance of the drug at the appearance of confusion. A 69-year-old Negro also developed a mild psychosis at a thiocyanate serum level of only 12.6 mg. per cent, when the drug was discontinued. Neither of these patients presented any signs of serious renal damage at the time of onset of thiocyanate therapy; maximum specific gravities were 1.018 and 1.022, and urea clearances 64 and 78 per cent of normal, respectively. On the other hand, two patients, receiving 0.2 Gm. of potassium thiocyanate three times daily, developed temporary blood serum levels over 25 mg. per cent without symptoms of any sort.

Hematologic studies under the direction of Dr. W. C. Levin yielded negative results concerning the effects of potassium thiocyanate upon the blood platelets, bleeding and coagulation times, prothrombin time, and rapidity and completeness of clot retraction. Further investigation is needed for explanation of the reported complication of potassium thiocyanate therapy, thrombophlebitis,¹⁴ which we did not find in our series. Occasional slight anemia resulted from prolonged thiocyanate therapy. Serial electrocardiograms, venous pressures, and circulation times (thiamine) showed no significant changes. Preliminary studies also have failed to reveal marked changes in serial inulin or diodrast renal clearances in our patients treated with potassium thiocyanate.

COMMENT

We are faced with a choice between the clinical impression of the apparent general inefficacy of potassium thiocyanate in relieving symptoms or of markedly surpassing the blood pressure-lowering effect of a placebo and other drugs, and the statistical evidence that exhibition of potassium thiocyanate is followed by more than chance lowering of blood pressure in comparison with other drugs. The majority of clinical reports and surveys,^{6-8,15-23} though they lack adequate controls, have come to more unequivocal conclusions, namely, that potassium thiocyanate does relieve symptoms, as it drops elevated blood pressure. Thus, Barker and associates,⁸ in their extensive experience, have noted hypotensive as well as favorable symptomatic effects of potassium thiocyanate in 47.5 per cent of cases, purely hypotensive effects in an additional 19.5 per cent, and symptomatic relief in 9 per cent more. In fairness to these investigators it should be pointed out that our serum thiocyanate values rose higher than the recommended ones of 8 to 12 or 5 to 15 mg. per cent. Yet complaints were present or increased in one-half of our thiocyanate-treated patients with serum values below 15 mg. per cent. The differentiation of hypertensive or neurotic symptoms from toxic effects of potassium thiocyanate is admittedly very difficult. Comparisons are possible in our study, however, with the more favorable symptomatic effects of the other drugs.

In view of the reported lowering of blood pressure by 30 to 60 mm. for long periods by two Russian investigators,²⁴ following six to eight injections of distilled water, such claims as successful hypotensive and symptomatic results in one-half of a group of selected hypertensives from intramuscular injections of pitressin tannate in oil²⁵ must be viewed with scepticism. Most reports of various modes of therapy similarly claim improvement in approximately one-half of the patients.

The possible hypotensive effects of the various drugs are to be interpreted also in the light of the conduct of our study. It is undeniably true, as in the case of hypnotic doses of oral and intravenous barbiturates²³ and the usual doses of various nitrites,²⁵ that the immediate effect of single or consecutive doses of some drugs is definitely hypotensive. We have made no effort to measure the immediate effects of the six drugs except by taking the blood pressures approximately two hours after their administration in the morning. We measured what may be called the average effect of their prolonged administration. This has the virtue of practicality in judging their efficacy in the management of essential hypertension in the clinic, but the disadvantages of possibly missing their temporary hypotensive effect.

With these reservations, we may conclude that some degree of lowering of blood pressure generally followed the exhibition of all six drugs; that differences in hypotensive effect were difficult to judge clinically, but statistically favored potassium thiocyanate administration; that the diastolic hypotensive effects of potassium thiocyanate were, at least in part, dependent on its high serum levels with their attendant toxic effects.

It is impossible to state with finality from our figures that the toxic effects of potassium thiocyanate, presumably on the cardiovascular as well as other systems, are responsible for its hypotensive effects. Such characterizations have been made for thiocyanate action in human²⁷ as well as animal subjects.⁹ The dangers of severe toxicity, even at low serum levels²⁵ due in part to marked variations in urinary output,^{8,14} have also been emphasized. The actual mode of pharmacologic action of potassium thiocyanate is far from clear. The finding of depression of liver oxidation¹⁵ needs further elucidation. Studies of its effect upon the cardiac metabolism and cardiac output, blood volume, and blood vascular system are in order. The demonstration of occasional increase in cutaneous lymphatic flow¹⁶ may indicate relaxation of arteriolar spasm, but more direct evidences of vasodilation are lacking. No increases in skin temperatures or oscillometric arterial pulsations occurred after the administration of potassium thiocyanate, nor did orthostatic hypotension or carotid sinus hypersensitivity develop, even in the two cases presenting syncopal attacks.²⁹ Preliminary studies also show negative effects of potassium thiocyanate upon the renal clearances of human hypertensives at therapeutic blood levels.²⁹ In view of the occurrence of diuresis at toxic levels,⁸ animal studies of renal clearances as affected by toxic doses of potassium thiocyanate are in order. In this connection, work in progress in our Department of Pharmacology³⁰ suggests a depressive influence of potassium thiocyanate in some of our hypertensive patients on the blood potassium level, at least upon its initial administration (Table V).

TABLE V. EFFECT OF LARGE DOSES OF POTASSIUM THIOCYANATE UPON THE SERUM POTASSIUM IN A HYPERTENSIVE PATIENT. MARKED FALL OF POTASSIUM UPON INITIAL ADMINISTRATION, NO DEPRESSION UPON SUBSEQUENT USE OF POTASSIUM THIOCYANATE. (E. A. C., WHITE FEMALE, AGED FORTY-SEVEN YEARS)

DATE	BLOOD PRESSURE	R _x	POTASSIUM THIOCYANATE LEVEL MG. PER CENT	K/LEVEL MG. PER CENT
8/27/46	250/130	None	0	21.85
9/16/46	180/110	0.8 Gm. Potassium thiocyanate Q. D.	34.4 (Toxic)	12.2
9/23/46	200/100	Off Potassium thiocyanate 7 days	15.0	14.0
10/11/46	220/115	Off Potassium thiocyanate 17 days	5.02	23.5
10/17/46	190/110	Off Potassium thiocyanate 23 days	0.8 mg.	23.1
11/ 1/46	210/110	Off Potassium thiocyanate 30 days	0.4 mg.	19.2
11/ 8/46	190/105	0.8 Gm. Q. D. 7 days	26.2 mg.	19.7
11/15/46	190/115	Reduced 0.6 Gm. Q. D.	22.4 mg.	21.5
11/21/46	190/120	0.6 Gm. Q. D. 14 days	18.2 mg.	25.2

SUMMARY AND CONCLUSIONS

1. A critically controlled study has been made of the effects of six commonly used types of drugs in human essential hypertension. Potassium thiocyanate was compared, under similar conditions and in the same sixty-eight patients, with five other drugs, including a placebo.

2. The best symptomatic relief was obtained from the administration of a placebo or niacin. Glucophylline, phenobarbital, and mannitol hexanitrate decreased the complaints of fewer patients and increased the symptoms in more cases than the placebo or niacin. Potassium thiocyanate, on the other hand, maintained or increased patients' complaints in almost one-half of the cases, and decreased them in less than one-third. Increase of symptoms undoubtedly occurred more frequently at serum thiocyanate levels above 15 mg. per cent, but was also frequent and, at times, perilous at the more commonly accepted "therapeutic" levels.

3. Hypotensive effects were demonstrable in many cases following the administration of all six drugs, including the placebo. The psychic calming effects of the physician's care and drug administration have been repeatedly emphasized and thus find further corroboration. All drugs, including potassium

thiocyanate, have been followed in some cases by actual rises in blood pressure or no change. Statistically, it has been possible to demonstrate that the thiocyanate period of therapy, when compared with the placebo therapy interval, showed significant drops in systolic and diastolic blood pressures, probably due to thiocyanate administration. Again, the diastolic pressures, at least, fell more markedly at serum levels of potassium thiocyanate above rather than below 15 mg. per cent.

4. Further studies are necessary to elucidate the mode of action of potassium thiocyanate, and to determine with finality whether its hypotensive effects occur at "toxic" or "therapeutic" blood levels. It would seem from our study that its administration is clinically hazardous and unreliable. The occasional marked drop in blood pressure due to potassium thiocyanate may, apart from any toxicity, cause relative cerebral, renal, and myocardial ischemia, and, possibly, other untoward effects in an organism accustomed to a high intra-arterial tension. The role that the inconstant hypotension produced by potassium thiocyanate may play in the prevention of cerebral hemorrhage or of cardiac hypertrophy and failure is not established from present-day data.

5. Clinical reports of the efficacy of drugs and other methods in the treatment of hypertension must be viewed with scepticism, particularly in the absence of control observations.

REFERENCES

1. Ayman, David: Normal Blood Pressure in Essential Hypertension, *J. A. M. A.* 94:1214, 1930.
2. Ayman, David: An Evaluation of Therapeutic Results in Essential Hypertension. II. The Interpretation of Blood Pressure Reductions, *J. A. M. A.* 96:2091, 1931.
3. Ayman, David: An Evaluation of Therapeutic Results in Essential Hypertension. I. The Interpretation of Symptomatic Relief, *J. A. M. A.* 95:246, 1930.
4. Kapernick, John S.: The Blood Pressure in Essential Hypertension: Effect of Several Reputedly Hypotensive Drugs, *AM. HEART J.* 26:610, 1943.
5. Evans, W., and Loughnan, O.: The Drug Treatment of Hyperpiesia, *Brit. Heart J.* 1:199, 1939.
6. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, *J. A. M. A.* 106:762, 1936.
7. Forster, R. E.: The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension, *Am. J. M. Sc.* 206:668, 1943.
8. Barker, M. H., Lindberg, H. A., and Wald, M. H.: Further Experiences With Thiocyanates. Clinical and Experimental Observations, *J. A. M. A.* 117:1591, 1941.
9. Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension. XVII. Experimental Observations on the Treatment of Hypertension, *J. A. M. A.* 119:1192, 1942.
10. Caviness, V. S., Umphlet, T. L., and Royster, C. L.: Blood Pressure and Sulfocyanates (Thiocyanate), *Am. J. M. Sc.* 204:688, 1942.
11. Trasoff, A., and Schneeberg, N. G.: The Naturally Occurring Blood Sulfocyanates and Their Relation to Blood Pressure, *Am. J. M. Sc.* 207:63, 1944.
12. Elkington, J. R., and Taffel, M.: The Apparent Volume of Distribution of Sulfocyanate and of Sulfanilamide in the Dog, *Am. J. Physiol.* 138:126, 1942.
13. Standardization of Blood Pressure Readings. Joint Recommendations, etc., *AM. HEART J.* 18:95, 1939.
14. Koffler, A., and Freireich, A.: Thrombophlebitis as a Hitherto Unreported Complication of Thiocyanate Therapy, *Am. J. M. Sc.* 207:374, 1944.
15. Robinson, R. W., and O'Hare, J. P.: Further Experiences With Potassium Sulfocyanate Therapy in Hypertension, *New England J. Med.* 221:964, 1939.

16. Griffith, J. Q., Jr., Lindauer, M. A., Roberts, Ella, and Rutherford, R. B.: Studies of Criteria for Classification of Arterial Hypertension. VI. Treatment With Thiocyanate, *AM. HEART J.* 21:90, 1941.
17. Crockett, K. A., and Moensch, L. G.: Potassium Thiocyanate Treatment of Hypertension, *J. A. M. A.* 129:982, 1942.
18. Fanson, E., Kinsey, D., and Palmer, R. S.: Potassium Sulfocyanate Therapy in Essential Hypertension, *New England J. Med.* 229:540, 1943.
19. Blumenthal, G. S., and Wetherby, M.: Potassium Thiocyanate in Hypertension, *Minnesota Med.* 27:177, 1944.
20. Durant, T. M.: Thiocyanate Therapy in Hypertension, *Pennsylvania M. J.* 47:1077, 1944.
21. D'Silva, J. L., and Evans, G.: The Treatment of Arterial Hypertension With Potassium Thiocyanate, *Brit. J. Urol.* 16:1, 1944.
22. Ayman, David: Present Day Treatment of Essential Hypertension, *M. Clin. North America*, 28:1141, 1944.
23. Page, I. H., and Corcoran, A. C.: Arterial Hypertension, Chicago, 1945, The Year Book Publishers, Inc.
24. Ruskin, A.: A Review of Soviet Cardiology, *Am. Rev. Soviet Med.* 3:260, 1946.
25. Griffith, J. Q., Jr., Padis, N., and Anthony, E.: Selection of Patients With Arterial Hypertension for Treatment by Repeated Injections of Pitressin, *Am. J. M. Sc.* 212:31, 1946.
26. Weaver, G. C., Willis, J. H., and Hodge, H. C.: Effect on Blood Pressure of Normal Persons and Hypertensive Patients of Glyceryl Trinitrate, Sodium Nitrite, Erythrol Tetranitrate and Mannitol Hexanitrate, *AM. HEART J.* 28:601, 1944.
27. Herrmann, George R.: Synopsis of Diseases of the Heart and Arteries, ed. 3, St. Louis, 1944, C. V. Mosby Company.
28. del Solar, A., Dussaillant, G., Brodsky, M., and Rodriguez, G.: Fatal Poisoning From Potassium Thiocyanate Used in Treatment of Hypertension, *Arch. Int. Med.* 75:241, 1945.
29. Ruskin, A., and McKinley, W. F.: Unpublished observations.
30. Emerson, G. A., Ewing, P. L., and Brooks, B. F.: Unpublished observations.

AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

IV. THE EFFECT OF POSITION CHANGE ON THE RELATIONSHIPS OF THE Q-T AND THE T-P INTERVALS RESPECTIVELY TO THE CYCLE LENGTH (R-R INTERVAL)

ISADORE SCHLAMOWITZ, M.D.
NEW YORK, N. Y.

HAVING shown that there was a more or less predictable relationship between the Q-T interval and the cycle length, attempts were made to determine the effects of various factors on it. Among these was the effect of change of position. Lombard and Cope¹ studied the effect of position change on this relationship by recording cardiac systole and cycle length by means of mechanical devices. They found that it was disturbed by the shortening of systole out of proportion to the shortening of the cycle length as the position changed from recumbent to sitting. This was still more marked when the standing position was assumed. White and Mudd² studied the effect of position change on the ratio of the Q-T interval to the cycle length in the electrocardiograms of five normal subjects. They found that there was a shortening of Q-T and C (cycle length) as the position was changed from supine to sitting and then to standing. However, no disturbance of the ratio was observed. Cheer and Li,³ in a study of 224 subjects, found that with a change of position from supine to sitting there was a disturbance of the $\frac{Q-T}{\sqrt{C}}$ ratio. The disturbance consisted of a shortening of the Q-T interval out of proportion to the shortening of the cycle length. Thus, $\frac{Q-T}{\sqrt{C}}$ became smaller when the position was changed from the supine to sitting. The difference, however, was not statistically significant. White, Kossmann, and Ershler⁴ found that $\frac{Q-T}{\sqrt{C}}$ became smaller when the position was changed from supine to sitting. However, they too found that the difference was not statistically significant. The effect of changing position on the relationship of the T-P interval to the cycle length does not appear to have been reported.

Since there appeared to be disagreement concerning the effect of position change on the Q-T to C relationship, and since the effect of position change on

From the Department of Therapeutics, New York University College of Medicine.
Received for publication Jan. 22, 1947.

the T-P to C relationship had not been reported before, it was decided to investigate these relationships.

METHOD

Fifty-three male medical students who were found to be normal were included in this series. The subject was considered normal only when the history, physical examination, chest fluoroscopy, and exercise tolerance test failed to reveal any evidence of the presence, past or present, of rheumatic fever, cardiac dysfunction, both organic and functional, circulatory disturbances, and other diseases.

The electrocardiograms were taken with a No. 2 Hindle string galvanometer with a string resistance of 2,200 ohms. The instrument was operated at 3 amperes, and the timer was checked and adjusted by means of a stroboscopic arrangement before each tracing was recorded. The timing error was therefore so minute that no corrections were necessary. The three standard limb lead tracings were standardized so that a string deflection of 1 cm. was equivalent to 1 millivolt.

An electrocardiogram was taken of each subject while he was in the supine position. Then, the subject sat up in a comfortable straight-backed arm chair. Another electrocardiogram was taken after he had been seated long enough for the heart rate to become stabilized again. This was necessary because it was found that upon sitting up there was a temporary increase in heart rate. This changing heart rate would have introduced effects that would have invalidated this study. This is more completely discussed in another article.⁵

The criteria for deciding that a tracing was normal and to be used in this study, as well as the method of measuring the Q-T interval, T-P interval, and C, are outlined in previous articles.^{6,7} The $K(Q-T)$ for the $\frac{Q-T}{C}$ relationship and the

$K(T-P)$ for the $\frac{T-P}{C}$ relationship for the supine as well as the sitting position were calculated in each case by introducing the Q-T and T-P and C values into the equations previously determined.^{6,7} These are:

$$K(Q-T) = \frac{Q-T - 0.167}{C} \quad \text{and} \quad K(T-P) = \frac{T-P + 0.267}{C}.$$

In Table I is listed the age distribution of the fifty-three subjects retained for this study.

RESULTS

In Table II are listed the $K(Q-T)$ values for both supine and sitting positions for each subject. In order to determine whether there was any significant difference between the two, the means for the $K(Q-T)$ for each position were calculated. It was found that the mean $K(Q-T)$ (supine) was 0.238, with a standard

TABLE I. AGE DISTRIBUTION

AGE (YR.)	NUMBER
19	2
20	5
21	12
22	17
23	12
24	3
25	0
26	1
27	0
28	0
29	0
30	1
Total	53

deviation of ± 0.025 . The mean K(Q-T) (sitting) was 0.237, with a standard deviation of ± 0.021 . The difference between the two means was 0.001. Although the difference appears small, it was felt that the t value should be determined to help in deciding how significant it was. Even a small difference might be significant, for in the presence of a high correlation between K(Q-T) (supine) and K(Q-T) (sitting) the difference between their means must be very small for it to remain without significance. This determination is briefly outlined as follows:

$$sd = \sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2} - 2r \frac{S_1 S_2}{N}}$$

$$r = \frac{\frac{\sum xy}{N} - M_1 M_2}{S_1 S_2}$$

$$r = +0.678$$

$$sd = 0.003$$

$$t = \frac{M_1 - M_2}{sd} = \frac{0.001}{0.003} = 0.333$$

sd = Standard error of the difference between the means.

S_1 = Standard deviation of mean K(Q-T) (supine).

S_2 = Standard deviation of mean K(Q-T) (sitting).

N, N_1, N_2 = Number of cases.

r = Coefficient of correlation between K(Q-T) (supine), K(Q-T) (sitting).

M_1 = Mean K(Q-T) (supine).

M_2 = Mean K(Q-T) (sitting).

Since t is so small, the difference between the means is not statistically significant.

In Table III are listed the K(T-P) values for both supine and sitting positions for each subject. In this instance the mean for K(T-P) (supine) was 0.693, with a standard deviation of ± 0.030 , and the mean for K(T-P) (sitting) was 0.694, with a standard deviation of ± 0.027 . The difference between the two means here was 0.001. This difference was tested as follows for significance for the reasons outlined previously:

TABLE II. COMPARISON OF THE VALUES FOR K(Q-T) IN THE SITTING AND IN THE RECUMBENT POSITIONS

NO.	CASE	RECUMBENT K(QT)	SITTING K(QT)
1	1002	.224	.230
2	1003	.261	.246
3	1004	.284	.281
4	1005	.208	.190
5	1006	.234	.230
6	1007	.209	.197
7	1008	.294	.267
8	1009	.229	.219
9	1010	.248	.230
10	1011	.220	.219
11	1012	.214	.249
12	1013	.257	.251
13	1014	.265	.262
14	1015	.190	.187
15	1016	.199	.220
16	1017	.258	.285
17	1018	.244	.231
18	1019	.251	.247
19	1020	.225	.221
20	1021	.237	.247
21	1022	.248	.222
22	1023	.228	.250
23	1024	.211	.224
24	1025	.220	.236
25	1026	.225	.233
26	1027	.248	.254
27	1028	.240	.209
28	1029	.251	.233
29	1030	.255	.241
30	1031	.219	.204
31	1032	.248	.256
32	1033	.234	.244
33	1034	.241	.229
34	1035	.282	.270
35	1036	.186	.216
36	1037	.267	.263
37	1038	.248	.245
38	1039	.257	.241
39	1040	.256	.261
40	1041	.224	.235
41	1042	.286	.262
42	1044	.215	.244
43	1045	.223	.247
44	1047	.263	.245
45	1048	.200	.221
46	1049	.220	.250
47	1050	.206	.217
48	1051	.208	.213
49	1052	.223	.240
50	1053	.294	.245
51	1054	.245	.248
52	1055	.249	.228
53	1056	.220	.244
Mean K(Q-T)		0.238	0.237
Standard deviation		± 0.025	± 0.021

TABLE III. COMPARISON OF THE K(T-P) VALUES IN THE SITTING AND IN THE RECUMBENT POSITIONS

NO.	CASE	RECUMBENT K(T-P)	SITTING K(T-P)
1	1002	.694	.687
2	1003	.681	.644
3	1004	.663	.660
4	1005	.705	.732
5	1006	.714	.708
6	1007	.723	.735
7	1008	.648	.707
8	1009	.659	.686
9	1010	.701	.722
10	1011	.672	.694
11	1012	.734	.672
12	1013	.642	.622
13	1014	.648	.671
14	1015	.756	.714
15	1016	.769	.728
16	1017	.712	.685
17	1018	.667	.690
18	1019	.648	.662
19	1020	.710	.714
20	1021	.719	.712
21	1022	.691	.720
22	1023	.694	.661
23	1024	.731	.711
24	1025	.645	.699
25	1026	.672	.678
26	1027	.693	.694
27	1028	.674	.688
28	1029	.642	.657
29	1030	.691	.691
30	1031	.729	.748
31	1032	.716	.688
32	1033	.689	.680
33	1034	.680	.706
34	1035	.662	.683
35	1036	.750	.728
36	1037	.674	.675
37	1038	.691	.691
38	1039	.659	.679
39	1040	.686	.671
40	1041	.680	.666
41	1042	.650	.682
42	1044	.679	.646
43	1045	.716	.681
44	1047	.667	.683
45	1048	.717	.700
46	1049	.729	.691
47	1050	.725	.716
48	1051	.750	.731
49	1052	.695	.770
50	1053	.716	.686
51	1054	.684	.713
52	1055	.694	.721
53	1056	.712	.692
Mean K(T-P)		0.693	0.694
Standard deviation		± 0.030	± 0.027

$$sd = \sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2} - 2r \frac{S_1 S_2}{N}}$$

$$r = \frac{\frac{\Sigma xy}{N} - M_1 M_2}{S_1 S_2}$$

$$r = +0.648$$

$$sd = 0.004$$

$$t = \frac{M_1 - M_2}{sd} = \frac{0.001}{0.004} = 0.250$$

sd = Standard error of the difference between the means.

S_1 = Standard deviation of K(T-P) (supine).

S_2 = Standard deviation of K(T-P) (sitting).

N, N_1, N_2 = Number of cases.

r = Coefficient of correlation between K(T-P) (supine) and K(T-P) (sitting).

M_1 = Mean K(T-P) (supine).

M_2 = Mean K(T-P) (sitting).

Since t is so small, the difference between the means is not statistically significant.

DISCUSSION

Apparently, the K(Q-T) and K(T-P) values expressing the relationship of Q-T and T-P to the cycle length respectively are not altered merely by changing the position of the subject. It should be noted that our subjects were allowed to remain in the sitting position until the heart rate had become stabilized before tracings were made. As will be pointed out in another report,⁵ the changing heart rate is an important factor and must be taken into account whenever the relationships of Q-T and T-P to the cycle length are studied. From these data and calculations it is also seen that there is a significant positive correlation between the K(Q-T) values for both positions, as well as between the K(T-P) values for both positions.

It should be mentioned here that the means for K(Q-T) and K(T-P) found in this series of fifty-three cases are significantly different from the corresponding means found in the previous study.^{6,7} However, all of the individual K(Q-T) and K(T-P) values as well as their means fall within the range for normal subjects found in the earlier study; that is, mean ± 2 standard deviation. A number of unavoidable factors entered into this study which are adequate to explain the differences. It is felt, nevertheless, that these deviations do not enter into the consideration of the problem investigated in the present study.

CONCLUSIONS

1. In normal young men there is a significant positive correlation between the K(Q-T) in the supine and sitting positions.
2. There is no significant difference between the K(Q-T) in the supine and sitting positions.
3. There is a significant positive correlation between the K(T-P) in the supine and sitting positions.
4. There is no significant difference between the K(T-P) in the supine and sitting positions.

The author wishes to thank Dr. Arthur C. DeGraff, Professor of Therapeutics at New York University College of Medicine, for having made this study possible and for his helpful suggestions.

REFERENCES

1. Lombard, W. P., and Cope, O. M.: Effect of Posture on the Length of the Systole of the Human Heart, *Am. J. Physiol.* 49:140, 1919.
2. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7:387, 1929.
3. Cheer, S. M., and Li, R. C.: Studies on the Electrical Systole (Q-T Interval) of the Heart. I. Duration of Electrical Systole in Normal Chinese, *Chinese J. Physiol.* 4:191, 1930.
4. White, M. S., Kossmann, C. E., and Ershler, I.: The Effect of High Altitude and Rebreathing on the Duration of Electrical Systole in Man, *AM. HEART J.* 24:230, 1942.
5. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. V. The Effect of Changing Heart Rate Upon the Q-T Interval and the T-P Interval and Their Respective Relationships to the Cycle Length (R-R Interval). *AM. HEART J.* In press.
6. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. I. The Duration of the Q-T Interval and Its Relationship to the Cycle Length (R-R Interval), *AM. HEART J.* 31:329, 1946.
7. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. II. The Duration of the T-P Interval and Its Relationship to the Cycle Length (R-R Interval), *AM. HEART J.* 31:464, 1946.
8. Snedecor, G. W.: Statistical Methods, ed. 3, Ames, 1940, The Iowa State College Press.

HEART DISEASE IN THE SOUTH

II. A STATISTICAL SURVEY OF ONE HUNDRED SEVENTEEN DEATHS DUE TO RHEUMATIC HEART DISEASE

JOE E. HOLOUBEK, M.D., AND ALICE BAKER HOLOUBEK, M.D.
SHREVEPORT, LA.

THE prevalence of rheumatic heart disease, particularly in the South, has been the subject of many reports.¹⁻¹⁰ A statistical analysis of 1,045 deaths due to heart disease from the autopsy records of Charity Hospital, New Orleans, La., has been previously reported by one of us (A. B. H.).¹ Because of the large number of deaths recorded due to rheumatic heart disease, a more detailed analysis of these deaths is now presented.

During the period which this study covered 8,313 patients were autopsied, of whom 5,252, or 63.2 per cent, were Negroes. The series included 2,982 Negro men, 2,270 Negro women, 1,975 white men, and 1,086 white women. Death was the result of heart disease in 1,045, or 12.6 per cent, of this entire series. Negroes comprised 63.6 per cent of this latter group.

Of the total group of cardiac deaths, 117, or 11.1 per cent, were classified as due primarily to rheumatic heart disease. This comprises 1.4 per cent of the total autopsy series (Fig.1). As will be seen by the chart, the peaks of incidence occurred between the ages of 10 and 20 years, after which there was a gradual decline. A second peak occurred at the age of 60 years.

Fig. 2 subdivides the incidence of deaths due to rheumatic heart disease into the incidence in the Negro and the incidence in the white race. There were sixty-seven, or 57.3 per cent, deaths in the Negroes, while the remaining fifty were in white persons. It will be seen that the peaks of incidence in the white race occur between the ages of 20 and 25 years; a second peak occurring at 60 years of age. However, in the Negro the peak occurred at the age of 15 years; with another peak present at 45 years. Of the white patients in this group thirty-three were men and seventeen were women. Of the Negro patients thirty-four were men and thirty-three were women.

Other Cardiac Findings and the Site of Valvular Involvement.—Complicating cardiac conditions in the entire group of 117 whose deaths were due to rheumatic heart disease were twenty-one cases of bacterial endocarditis (17.9 per cent), sixteen subacute and five acute; eleven cases of coronary sclerosis; and five cases of hypertension.

From the Department of Medicine of the Louisiana State University School of Medicine, and the Charity Hospital at New Orleans.
Received for publication Jan. 16, 1947.

TOTAL DEATHS DUE TO RHEUMATIC HEART DISEASE

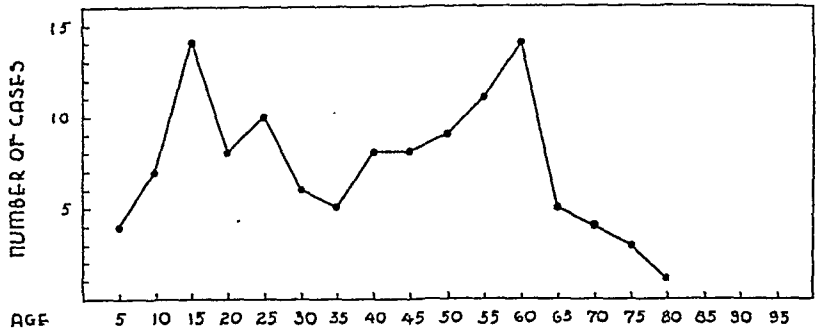


Fig. 1.

INCIDENCE OF DEATH DUE TO RHEUMATIC HEART DISEASE

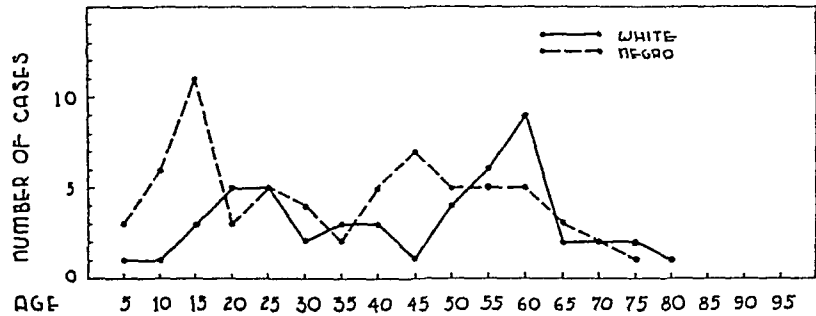


Fig. 2.

INCIDENCE OF MITRAL LESIONS IN DEATHS DUE TO RHEUMATIC HEART DISEASE

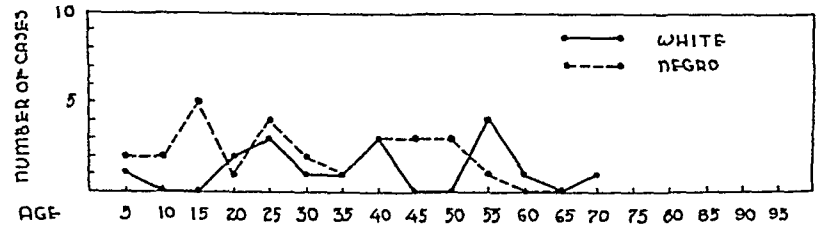


Fig. 3.

INCIDENCE OF COMBINED MITRAL AND AORTIC LESIONS IN DEATH DUE TO RHEUMATIC HEART DISEASE

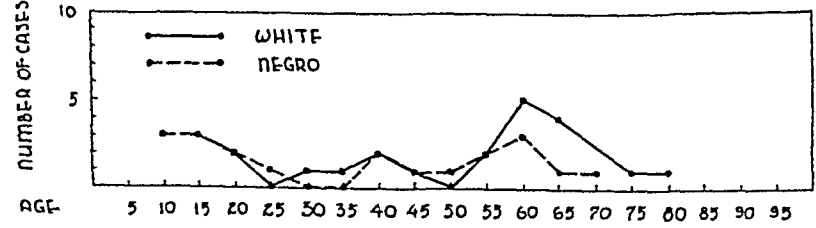


Fig. 4.

The site of the cardiac involvement by the rheumatic process is shown in Table I. It will be seen that mitral involvement alone was present in the highest percentage of cases.

Further subdividing of the valvular involvement reveals the number of times each valve was involved in the 117 subjects whose deaths were due to rheumatic heart disease. The mitral valve was involved in ninety-six (82 per cent) of these cases, the aortic in sixty (51.2 per cent), the tricuspid in eleven (9.4 per cent), and the pulmonary valve in three (2.5 per cent). There was no definite difference in racial incidence in this particular group (Table II).

TABLE I. SITES OF RHEUMATIC VALVULAR INVOLVEMENT IN ONE HUNDRED SEVENTEEN DEATHS DUE TO RHEUMATIC HEART DISEASE

VALVE	WHITE			NEGRO			GRAND TOTAL	PER CENT
	M	F	TOTAL	M	F	TOTAL		
Mitral	9	8	17	11	18	29	46	39.3
Mitral and aortic	16	7	23	11	7	18	41	35.0
Aortic	4	1	5	6	1	7	12	10.2
Mitral and tricuspid	1	0	1	2	1	3	4	3.4
Mitral, tricuspid, and aortic	1	0	1	2	1	3	4	3.4
Pancarditis	0	1	1	0	3	3	4	3.4
Myocarditis	0	0	0	1	1	2	2	1.7
Aortic, pulmonary, and tricuspid	0	0	0	1	1	2	2	1.7
Mitral and pulmonary	1	0	1	0	0	0	1	0.8
Aortic and tricuspid	1	0	1	0	0	0	1	0.8

TABLE II. INCIDENCE OF VALVULAR INVOLVEMENT IN ONE HUNDRED SEVENTEEN DEATHS DUE TO RHEUMATIC HEART DISEASE

VALVE	WHITE			NEGRO			GRAND TOTAL	PER CENT
	M	F	TOTAL	M	F	TOTAL		
Mitral	28	15	43	26	27	53	96	82.0
Aortic	22	8	30	20	10	30	60	51.2
Tricuspid	3	0	3	5	3	8	11	9.4
Pulmonary	1	0	1	1	1	2	3	2.5

Mitral Involvement: Pure mitral lesions were present in forty-six subjects. In nine there was an associated subacute bacterial endocarditis; in one, acute bacterial endocarditis; in one, rheumatic pneumonia; and in one, coronary sclerosis. There was practically no difference according to race or sex (Fig. 3).

Mitral and Aortic Involvement: In this survey involvement of both the mitral and aortic valves was found frequently, being present in a total of forty-one cases. Complicating factors in this group were: subacute bacterial endocarditis in four cases, acute bacterial endocarditis in four cases, coronary sclerosis in three cases, and hypertensive heart disease in one case. Again there was very little difference in the racial or sexual incidence (Fig. 4).

Aortic Valvular Involvement: There were twelve cases in which the aortic valve only was involved. In all of these there was marked hypertrophy and dilatation of the left ventricle. The majority of these were found in middle-aged subjects, the oldest being 98 years old, and the youngest 27 years of age. One of these had acute endocarditis, two had arteriosclerosis, and two had hypertensive heart disease (Fig. 5).

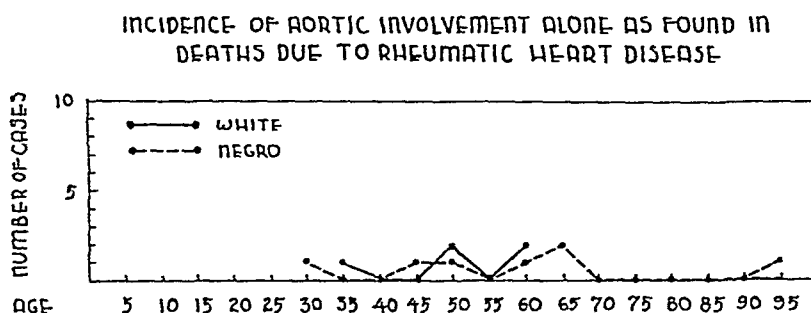


Fig. 5.

Mitral and Tricuspid Involvement: Mitral and tricuspid involvement was present in only four cases; a white boy, 8 years old, two male Negroes, 11 and 32 years of age, and one Negro woman, 32 years of age. One of the Negro patients had associated syphilitic aortitis.

Mitral, Tricuspid, and Aortic Involvement: Combined mitral, tricuspid, and aortic lesions were present in one 58-year-old white man, in two Negro men, 29 and 54 years of age, respectively, and in one 11-year-old Negro girl.

Pancarditis: Pancarditis was present in one white girl, 17 years of age, and in three Negro women, 12, 41, and 54 years of age, respectively.

Myocarditis: Rheumatic myocarditis alone was present in two Negro patients; one boy, 5 years of age, and one girl, 9 years of age. In both of these the valves were normal.

Aortic, Pulmonary, and Tricuspid Involvement: Combined aortic, pulmonary, and tricuspid involvement was present in two instances; one 59-year-old Negro man, and one 11-year-old Negro girl.

Mitral and Pulmonary Involvement: Mitral and pulmonary valve involvement was present in one white boy, 5 years of age.

Aortic and Tricuspid Involvement: Aortic and tricuspid involvement was present in one white man whose age was 48 years.

COMMENT

Negroes comprised 63.2 per cent of the entire series of autopsied patients. This figure compares almost identically with the percentage of Negroes (63.6 per cent) in the series whose death was due to heart disease. These percentages likewise compare closely with the percentage (57.3 per cent) of Negroes dying of rheumatic heart disease.

The incidence of deaths due to rheumatic heart disease in white subjects showed a ratio of 2 men to 1 woman, while in Negroes this ratio was 1:1. In the total series of autopsied patients, the incidence of men to women was almost 2:1 in white subjects and 1.33:1 in Negroes.

The separation of the deaths due to rheumatic heart disease into the racial incidence reveals that the high peak of deaths in the young group was due to the large number of deaths in Negro girls between the ages of 10 and 15 years. This confirms the statement of Decherd and Herrmann⁵ that there is a high incidence of rheumatic heart disease in young Negroes.

The incidence of the valvular involvement follows approximately the same general trend that has been found elsewhere in the country, although the incidence of isolated involvement of the aortic valve is slightly higher in this survey. The mitral valve was, of course, the most commonly involved.

In comparing the age at death of the group having only mitral involvement with that of the group with both mitral and aortic involvement, it will be seen that in the latter group death came at a slightly later age than in the former group.

SUMMARY

In a series of 8,313 patients who were necropsied, death was found to have been the result of heart disease in 1,045 patients. In 117, rheumatic heart disease was present. This series of 117 subjects whose deaths were due to rheumatic heart disease has been analyzed according to sex, age, and racial incidence, and the type of valvular involvement.

The members of the Pathology Department of the Hospital and of the Louisiana State University School of Medicine were very cooperative, and assisted in the study of records which proved difficult to interpret.

Dr. DeWitt T. Baker, New Orleans, assisted in compiling some of the statistical data.

REFERENCES

1. Holoubek, Alice B.: Heart Disease in the South, *AM. HEART J.* 29:168, 1945.
2. Camp, P. D., and Glavin, Louise: Rheumatic Fever and Rheumatic Heart Disease in Virginia, *Virginia M. Monthly* 70:397, 1943.
3. Baker, L. A.: Analysis of the Etiology in 815 Cases of Organic Heart Disease, *Med. Bull. of Veteran's Administration* 18:254, 1942.

4. Claiborne, T. S., and Wolff, B. P.: Rheumatic Heart Disease, *South. M. J.* 34:684, 1941.
5. Decherd, G. M., and Herrmann, G. R.: Rheumatic Heart Disease in Texas, *Texas State J. Med.* 39:229, 1943.
6. White, P. D.: Heart Disease, ed. 2, New York, 1938, The Macmillan Company.
7. Rowe, Paul: Valvular Heart Disease, *Journal Lancet* 62:218, 1942.
8. Shown, A. N.: Rheumatic Heart Disease in Arizona, *Southwestern Med.* 27:140, 1943.
9. Hardin, B. L., and Daniels, W. B.: Tricuspid Stenoses, *Ann. Int. Med.* 17:536, 1944.
10. Clawson, B. J.: Incidence of Heart Disease Among 30,265 Autopsies, With Special Reference to Age and Sex, *AM. HEART J.* 29:607, 1941.

HEART DISEASE IN THE SOUTH

III. AN ANALYSIS OF TWO HUNDRED SEVENTEEN DEATHS DUE TO ARTERIOSCLEROTIC HEART DISEASE

JOE E. HOLOUBEK, M.D., AND ALICE BAKER HOLOUBEK, M.D.
SHREVEPORT, LA.

THERE have been many statistical analyses of coronary arteriosclerosis.¹⁻¹⁹ It is evident that in most of these the highest incidence of death from arteriosclerotic cardiovascular disease has been found to occur in the fifth and sixth decades. Most of these studies consider the sexual distinctions in incidence, but few have studied the racial differences.

MATERIAL AND FINDINGS

The material in this paper was gathered from the autopsy records of Charity Hospital at New Orleans from 1935 through 1940. A total of 8,313 autopsies were performed during this period. In 1,045, or 12.6 per cent, of this series death was due primarily to heart disease.

Table I shows the racial and sexual distribution of the total autopsied cases and of the patients whose deaths were due to heart disease. The male sex comprised 67 per cent of the total deaths due to heart disease and 59.6 per cent of the total number of autopsies. Of the cardiac deaths, 217, or 20.7 per cent, were considered to be due primarily to arteriosclerotic heart disease. This comprises 2.6 per cent of the total number of autopsies. The age at death ranged from 30 to 95 years, with the greatest incidence between the ages of 50 and 75 years (Fig. 1).

Fig. 2 illustrates the age at death in white as compared with Negro subjects. One hundred twenty-nine, or 59.4 per cent, of the 217 deaths occurred in the white race, the highest incidence occurring between the ages of 55 to 75 years. In the Negro race the peak incidence occurred between the ages of 45 and 60 years.

Of the group whose deaths were due to arteriosclerosis of the heart and aorta, 117 (53.9 per cent) showed pathologic evidence of myocardial infarction and/or coronary occlusion (Fig. 3). The age range in this group was from 30 to 80 years, with the peak between the ages of 45 and 65 years. In the group whose deaths were due to arteriosclerotic cardiovascular disease without myo-

From the Department of Medicine of the Louisiana State University School of Medicine and the Charity Hospital at New Orleans.

Received for publication Jan. 16, 1947,

AGE AT DEATH OF 217 FATAL CASES OF ARTERIOSCLEROTIC HEART DISEASE

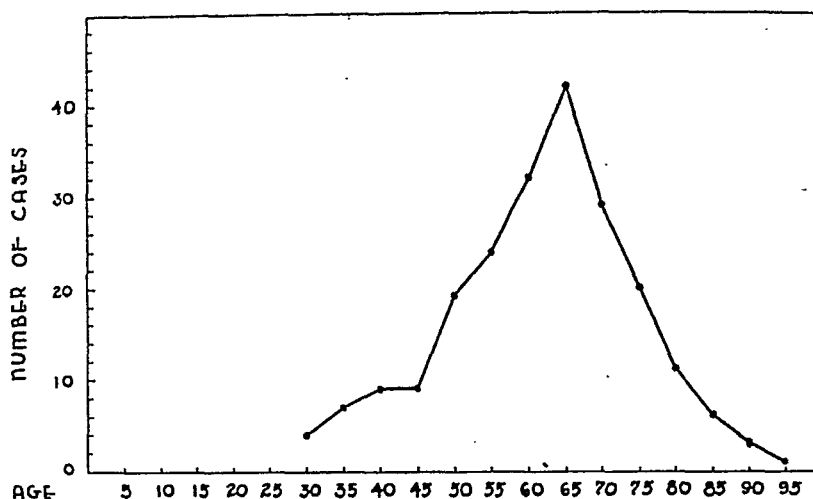


Fig. 1.

INCIDENCE OF DEATH DUE TO ARTERIOSCLEROTIC HEART DISEASE

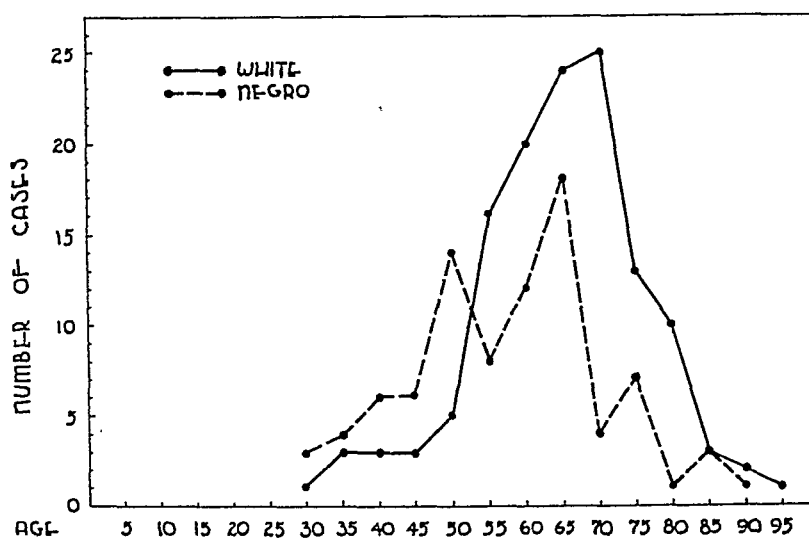


Fig. 2.

ARTERIOSCLEROTIC HEART DISEASE (BOTH RACES) SHOWING THOSE WITH AND THOSE WITHOUT MYOCARDIAL INFARCTION

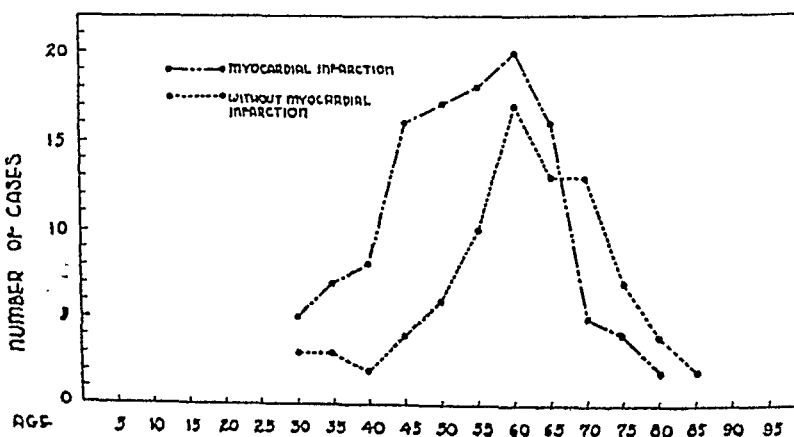


Fig. 3.

TABLE I. RACE AND SEX INCIDENCE IN ROUTINE AUTOPSIES AND IN AUTOPSIES ON PATIENTS WHOSE DEATH WAS THE RESULT OF HEART DISEASE

	NEGRO				WHITE				GRAND TOTAL
	M	F	TOTAL	PER CENT	M	F	TOTAL	PER CENT	
Routine autopsies	2,982	2,270	5,252	63.2	1,975	1,086	3,063	36.8	8,313
Deaths due to heart disease	423	242	665	63.6	281	99	380	37.4	1,045

cardial infarction and/or coronary occlusion, the age at death ranged from 30 to 85, with the greatest incidence between the ages of 55 and 75 years.

In a further study of the 117 autopsied patients who died of myocardial infarction, race and sex are considered. Seventy-three (61.7 per cent) of this group of 117 patients were white persons (Fig. 4.). In this group the age at death in white persons ranged from 30 to 80 years and in Negroes from 30 to 65 years. The highest incidence in white subjects was between the ages of 50 to 65 and in the Negroes between 45 to 60 years.

In differentiating the deaths according to sex (Fig. 5), it is seen that the ratio of men to women is about 7 to 3. There is a rise in incidence in the male group at the age of 30, with a peak occurring between the ages of 55 and 60 years. In the female group there is a rise in incidence at the age of 45 which is maintained until the age of 70 years.

A further differentiation, (Figs. 6 and 7) shows that in the white race there were fifty-five men with autopsy evidence of myocardial infarction as compared to eighteen women. In the women of this series there is very little change in incidence of myocardial infarction throughout the different age groups. However, in the men, there is a marked rise in incidence between the ages of 50 and 65 years. In the Negroes of this series, twenty-seven of the forty-four deaths due to myocardial infarction occurred in men. The incidence of myocardial infarction in Negro women varied only slightly in different age groups. In the male group, however, the incidence reached a peak between the ages of 45 and 55 years.

Of the 117 cases who died of coronary occlusion, hypertension occurred in thirty-five, rheumatic heart disease in three, syphilitic heart disease in two, and diabetes mellitus in one.

Of particular interest were the examples of coronary occlusions which occurred in patients below the age of 40 years. Twelve such cases were found in this study: six in Negro men, two in Negro women, two in white men, and two in white women. The ages of the Negro men were 30, 31, 38, 40, 40, and 40 years, respectively, Negro women, 30 and 35 years, white men, 31 and 32 years, and white women, 35 and 37 years. Hypertension was present in five of these patients, and rheumatic heart disease in two.

There were 100 deaths due to arteriosclerotic heart disease without evidence of myocardial infarction (Figs. 8 and 9). Included in this group were eleven

MYOCARDIAL INFARCTION SHOWING RACIAL INCIDENCE

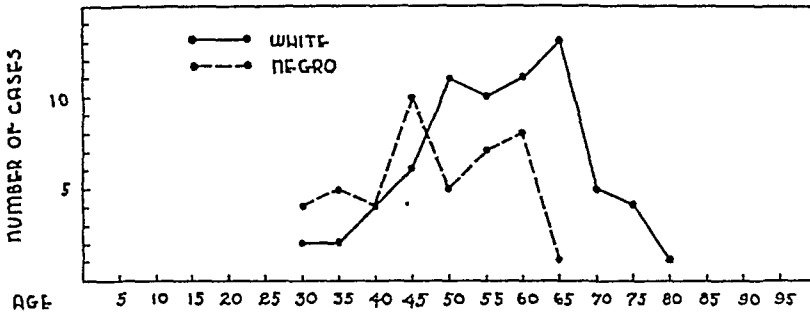


Fig. 4.

MYOCARDIAL INFARCTION IN BOTH RACES

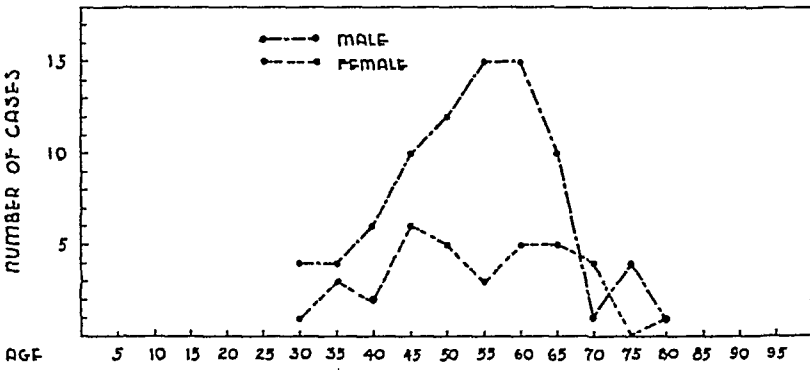


Fig. 5.

MYOCARDIAL INFARCTION IN THE WHITE RACE

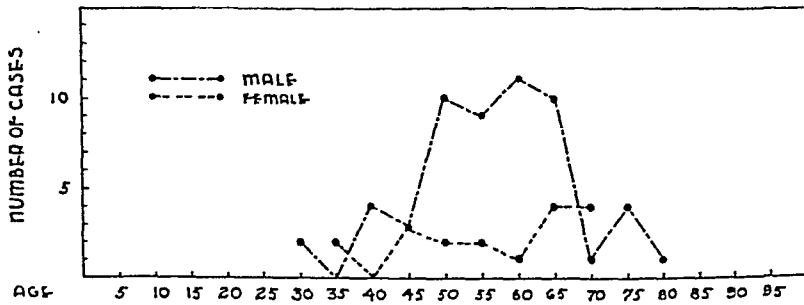


Fig. 6.

MYOCARDIAL INFARCTION IN THE NEGRO RACE

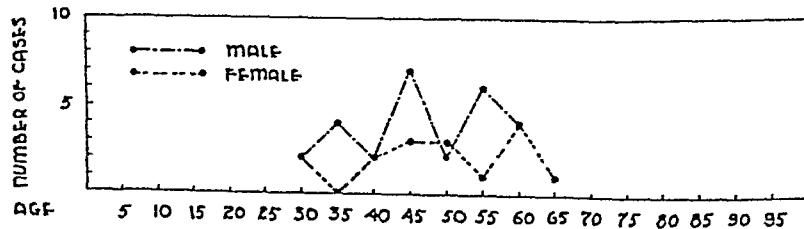


Fig. 7.

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION SHOWING RACIAL INCIDENCE

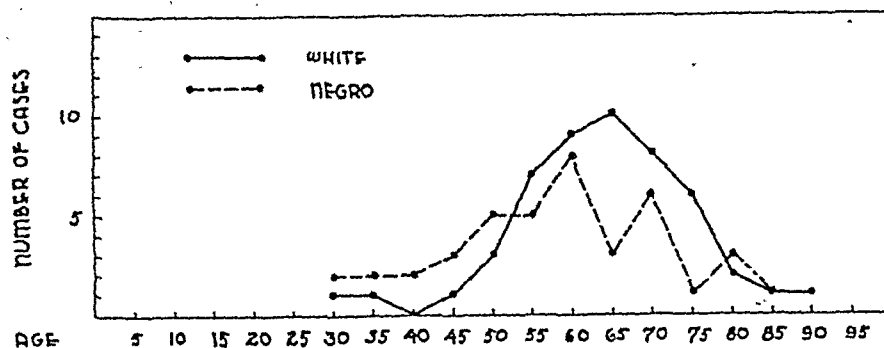


Fig. 8.

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION SHOWING SEX INCIDENCE

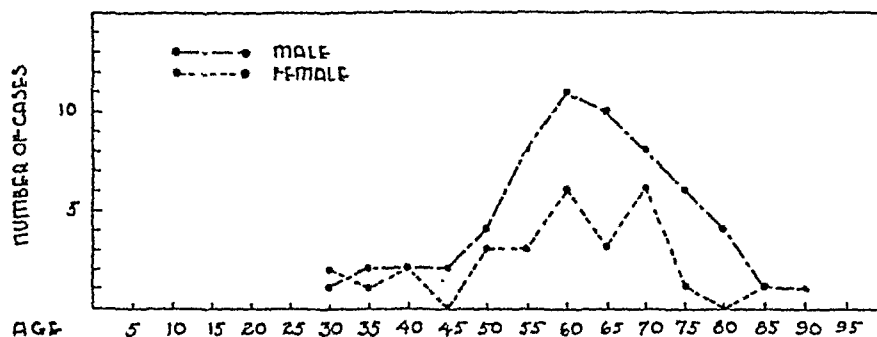


Fig. 9.

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION IN NEGROES

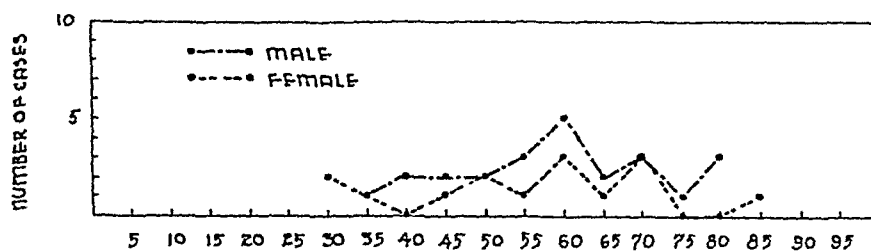


Fig. 10.

ARTERIOSCLEROTIC HEART DISEASE WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION IN WHITE PATIENTS

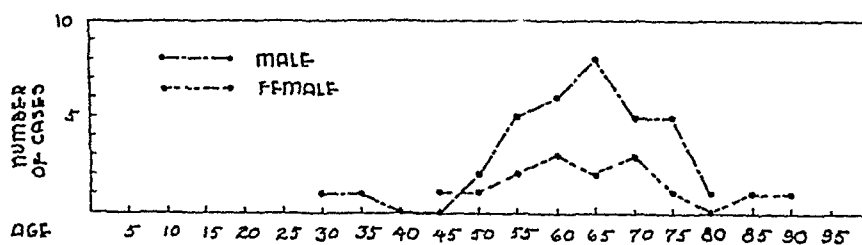


Fig. 11.

cases who died of dissecting aneurysm of the aorta. This comprised 5.1 per cent of the total deaths due to arteriosclerotic cardiovascular disease. These cases of dissecting aneurysm of the aorta have been thoroughly reviewed by Holland and Bayley.¹⁹ Of the eighty-nine remaining cases, fifty (56.1 per cent) were of the white race.

Fig. 10 depicts death due to arteriosclerotic heart disease without evidence of myocardial infarction in the Negroes of this series. There was very little difference in incidence in the two sexes in this group. The incidence showed a slight increase at the ages of 60 and 70 years in both races. In the white race (Fig. 11) it may be seen that thirty-six, 72 per cent, were males, and that the highest incidence in both races was between the ages of 60 and 70.

In the group whose death was due to arteriosclerotic cardiovascular disease without evidence of myocardial infarction the following complications were observed: hypertension in twelve cases, rheumatic heart disease in seven cases, syphilitic cardiovascular disease in one case, and Paget's disease in one case.

SUMMARY

A statistical analysis of 217 deaths due to arteriosclerotic cardiovascular disease at Charity Hospital has been presented and analyzed according to age, sex, and race.

The incidence of death from arteriosclerotic heart disease was found to be higher in the white race than in the Negro race. However, death from this cause occurred at an earlier age in Negroes of this series. Of particular interest is the relatively high incidence of myocardial infarction found in the Negro race, particularly in the younger age groups. The incidence was higher in the male sex in both races. In deaths due to infarction in the white race the ratio of men to women was 3:1, in the Negro race, 1.5:1. In both races the ratio was 2.3:1.

We are indebted to the members of the Pathology Department of the Hospital and of the Louisiana State University School of Medicine who were very cooperative and assisted in the study of records which proved difficult to interpret.

We are also indebted to Dr. DeWitt Baker for his assistance in compiling some of the statistical data.

REFERENCES

1. Holoubek, Alice B.: Heart Disease in the South, I., *AM. HEART J.* 29:168, 1945.
2. Gordon, W. H., Bland, E. F., and White, P. D.: Coronary Artery Disease, Analyzed Post Mortem, With Special Reference to the Influence of Economic Status and Sex, *AM. HEART J.* 17:10, 1939.
3. Baker, T. W., and Willius, F. A.: Coronary Thrombosis Among Women, *Am. J. M. Sc.* 196:815, 1938.
4. Glendy, E. R., Levine, S. A., and White, P. D.: Coronary Disease in Youth, *J. A. M. A.* 109:1775, 1937.
5. Wolferth, C. C.: Present Concepts of Acute Coronary Occlusion, *J. A. M. A.* 109:1769, 1937.
6. Goldsmith, Grace A., and Willius, F. A.: Bodily Build and Heredity in Coronary Thrombosis, *Ann. Int. Med.* 10:1181, 1937.
7. Willius, Frederick A.: Life Expectancy in Coronary Thrombosis, *J. A. M. A.* 106:1890, 1936.

8. Levy, Hyman, and Boas, E. P.: Coronary Artery Disease in Women, *J. A. M. A.* 107:97, 1938.
9. Levy, R. L., Bruenn, H. G., and Kurtz, Dorothy: Facts on Disease of the Coronary Arteries, Based on a Survey of the Clinical and Pathological Records of 762 Cases, *Am. J. M. Sc.* 187:376, 1934.
10. Willius, F. A., Smith, H. L., and Sprague, T. H.: Study of Coronary and Aortic Sclerosis; Incidence and Degree in 5,060 Consecutive Post Mortem Examinations, *Proc. Staff Meet., Mayo Clin.* 8:140, 1933.
11. Levy, R. L.: Mild Forms of Coronary Thrombosis, *Arch. Int. Med.* 47:1, 1931.
12. Conner, L. A., and Holt, Evelyn: The Subsequent Course and Prognosis in Coronary Thrombosis in an Analysis of 287 Cases, *AM. HEART J.* 5:705, 1930.
13. Levine, S. A.: Coronary Thrombosis, *Medicine* 8:245, 1929.
14. Christian, H. A.: Cardiac Infarction (Coronary Thrombosis), *AM. HEART J.* 1:129, 1925.
15. Nathanson, M. H.: Disease of the Coronary Arteries; Clinical and Pathological Features, *Am. J. M. Sc.* 170:240, 1925.
16. Wearn, Joseph T.: Thrombosis of the Coronary Arteries With Infarction of the Heart, *Am. J. M. Sc.* 165:250, 1923.
17. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *AM. HEART J.* 3:302, 1928.
18. Claswon, B. J.: Incidence and Types of Heart Disease Among 30,265 Autopsies, *AM. HEART J.* 22:607, 1941.
19. Holland, L. F., and Bayley, R. H.: Dissecting, Aneurysm, *AM. HEART J.* 20:223, 1940.

Clinical Reports

PAROXYSMAL AURICULAR TACHYCARDIA OF UNUSUAL TYPE

BENJAMIN R. GENDEL, M.D.*

MEMPHIS, TENN.

IN THE majority of instances paroxysmal auricular tachycardia conforms to a typical pattern. It is characterized by a sudden onset, a rapid, highly regular rate, usually between 160 and 180 per minute, and a sudden termination. The disturbed rhythm is transient, lasting from several seconds to a few days. Rarely, it may be prolonged to a few weeks. It may recur repeatedly over a short period of time but usually between attacks there is a prolonged interval which may last for days or years.

Not infrequently, variations from this pattern occur. Cases have been described in which there is slight irregularity of the rate associated with alteration of the cycle length.¹ This type of irregularity cannot be detected clinically. In other cases a more marked irregularity may be present due to auriculoventricular block. When this block is of varying degree, the condition clinically resembles auricular fibrillation. Literature on these cases has recently been reviewed by Barker and associates² and by Decherd and co-workers.³ Fine and Miller⁴ and Miller and Perelman⁵ reported two patients with an unusual variation, in both of whom paroxysmal auricular tachycardia was precipitated whenever the patient was erect and frequently would disappear on recumbency. These patients and some of those with block showed a persistence of the arrhythmia over a prolonged period of time.

Recently two patients were observed with an unusual type of paroxysmal auricular tachycardia. The rapid heart rate persisted over a period of months and was characterized by recurrent episodes of auricular tachycardia lasting a few seconds, with intervening periods of approximately one-half second between attacks. Because of the unusual nature of this arrhythmia, these cases are being reported.

REPORT OF CASES

CASE 1.—A 25-year-old white man who felt well was found to have an irregular tachycardia on routine examination on May 26, 1945. An electrocardiogram made on May 29, 1945, revealed the arrhythmia to be discussed. He was treated with quinidine sulfate, 0.2 Gm., and pheno-

From the Medical Service, Lovell General Hospital, Fort Devens, Mass.
Received for publication Oct. 17, 1946.

*Formerly Major, Medical Corps, Army of the United States.

barbital, 0.03 Gm., three times daily and later four times daily on several occasions without success. In July, another course of quinidine sulfate, 0.4 Gm., every four hours, was attempted but after several days it was discontinued because of nausea, vomiting, and diarrhea. There was no effect on the arrhythmia. Several courses of digitalis produced a 2:1 A-V block but did not affect the fundamental rhythm. The past and family histories were irrelevant.

The lungs were clear to percussion and auscultation. The pulse was rapid and irregular. The rate was 150 per minute at the wrist and 172 at the apex. The blood pressure was 120/80. The heart size was within normal limits, and there were no murmurs. The heart rate and irregularity did not change after exercise. The liver and spleen were not palpable, and there was no edema. No other significant findings were present.

The basal metabolic rate was -11 per cent. X-ray and fluoroscopic study revealed no enlargement of the heart or its chambers. Many electrocardiograms were taken during the patient's stay in the hospital. These revealed an auricular tachycardia with a rate of 162 to 175 per minute. The tachycardia occurred in short paroxysms lasting about five seconds. After a very brief interval of approximately 0.8 second, a normal sinus beat would occur and this would be followed by another short run of auricular tachycardia (Fig. 1, A).

The patient was observed for several weeks without medication. During this time he was able to carry out his routine activities and there was no suggestion of cardiac decompensation. The arrhythmia continued unabated and was present continuously. No change was induced by exercise, breath holding, change of position, or carotid sinus pressure. In September, 1945, he was fully digitalized with digitalis leaf and this caused a slowing of the ventricular rate due to 1:1 to 2:1 A-V block (Fig. 1, B). Digitalis was stopped and he was later given 25.0 mg. of mechoyl subcutaneously. A prompt effect was obtained, characterized by profuse sweating and suffusion of the face, chest, and arms, but there was no change in the fundamental rhythm. A course of quinidine, 0.4 Gm. every two hours orally for five doses, was given without effect. A course of potassium salts given orally for several days produced no effect. Digitaline Nativelle, 1.2 mg., was administered intravenously but there was no effect on the rhythm. Digitaline Nativelle, 0.1 mg. orally three times daily, was continued, and in several days 1:1 to 2:1 A-V block appeared. The patient was maintained on a dose of 0.1 Gm. of digitalis leaf, and on Dec. 18, 1945, he received a course of quinidine sulfate, 0.4 Gm. every two hours orally for five doses. That afternoon the rate and rhythm became normal, and an electrocardiogram disclosed the presence of a normal sinus rhythm. The patient was kept on a maintenance dose of digitalis, 0.1 Gm. daily, until Jan. 7, 1946, when it was discontinued. Subsequent electrocardiograms (Fig. 2) revealed a normal sinus rhythm with slight left axis deviation, slightly depressed S-T segments in Leads I, II, and III, and inverted T waves.

CASE 2.—A 25-year-old white man was found to have an arrhythmia when admitted to the hospital following an injury to the feet, incurred when he fell one and one-half stories to the ground. An electrocardiogram on July 14, 1945, showed the presence of an arrhythmia, to be discussed. The patient was totally unaware of this arrhythmia and had no symptoms referable to the cardiovascular system. Attempts to treat the arrhythmia with digitalis, quinidine, and carotid sinus pressure were unsuccessful. The past and family histories were irrelevant.

The blood pressure was 115/60. The heart was normal in size and position. The rate was 160 per minute and slightly irregular. The liver and spleen were not palpable, and there was no edema. The remainder of the examination was noncontributory.

The basal metabolic rate was normal. X-ray and fluoroscopic examinations of the heart were normal. Electrocardiogram revealed an arrhythmia which was interpreted to show short runs of paroxysmal auricular tachycardia lasting about four seconds, with an interval of 0.5 second between paroxysms. The heart rate was 190 per minute. The intermittence was not due to an A-V block and, unlike Case 1, normal sinus beats did not occur between the short paroxysms (Fig. 3, A).

The arrhythmia was not influenced by respiration, change in position, or carotid sinus pressure. The patient was digitalized orally with digitalis leaf with the production of A-V block, and, at times, interruption of the abnormal mechanism and the occurrence of normal sinus beats (Fig. 3, B). Digitalis was discontinued and the patient was later given a course of potassium

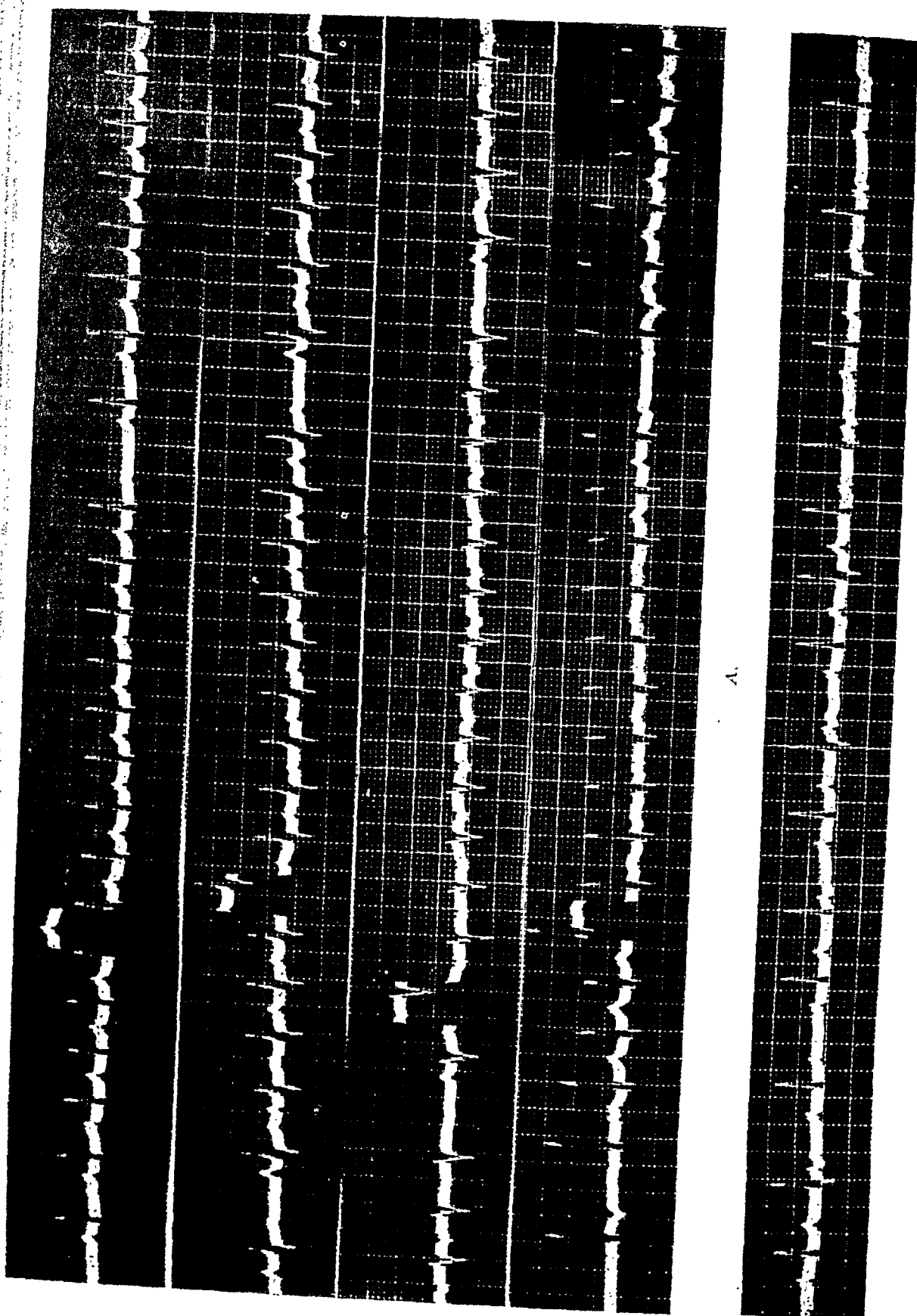


Fig. 1.—Case 1. A, Nov. 19, 1946. Three standard leads and Lead IV F. B, Dec. 15, 1946. Lead I. Auricular tachycardia with varying degrees of partial A-V block.

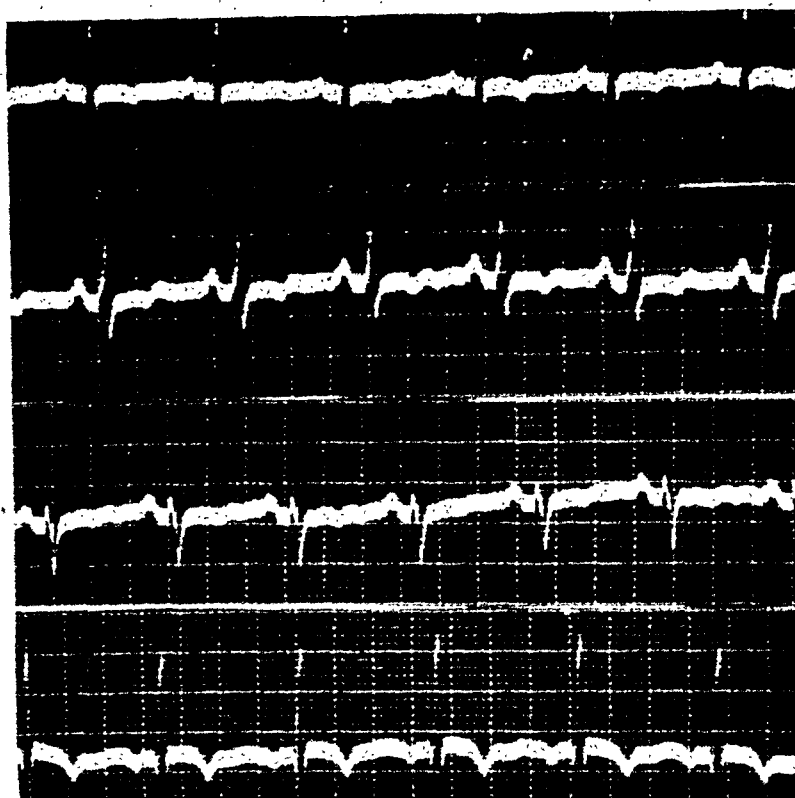


Fig. 2.—Case 1. Jan. 29, 1946. Normal sinus rhythm. There are still S-T segment abnormalities and T-wave inversion. The patient had not had digitalis for three weeks.

salts without any influence on the arrhythmia. On Dec. 6, 1945, he was given 25 mg. of mechohyl without any change.

He was given numerous trials of therapy with quinidine sulfate, 0.4 Gm. orally every two hours for five doses. These were invariably unsuccessful. On Jan. 28, 1946, after a course of quinidine, the patient developed a normal sinus rhythm with a rate of 77 per minute (Fig. 4). However, this was short-lived and the arrhythmia returned on the following morning. Further attempts with a similar course of quinidine, followed by 0.4 Gm. every four hours as a maintenance dose, were fruitless. On this regime, the patient developed A-V block and ventricular premature beats, the latter occurring in groups of two or three. It was felt that further quinidine might result in ventricular tachycardia and this therapy was discontinued. One cubic centimeter of prostigmine 1:2000 was administered subcutaneously without influence on the rhythm. The patient was given Cedilanid, 1.6 mg., intravenously in January, 1946, and this resulted in periods of asystole and auricular tachycardia with varying A-V block. While fully digitalized, another course of quinidine was attempted but did not restore a normal rhythm. The patient was kept on a maintenance dose of digitalis which was of value in that it reduced the ventricular rate.

DISCUSSION

The unusual arrhythmia presented by these two patients who were observed simultaneously had certain clinical characteristics. It was chronic and persisted over a period of months. Despite the persistent rapid cardiac rate, no signs of congestive failure developed although the patients were permitted ordinary activity. There was refractoriness to the usual therapy which is effective in paroxysmal auricular tachycardia. Breath-holding, the Valsalva experiment, change in posture, digitalis, quinidine, and time did not influence the fundamental arrhythmia. In the first patient it was possible after full digitalization

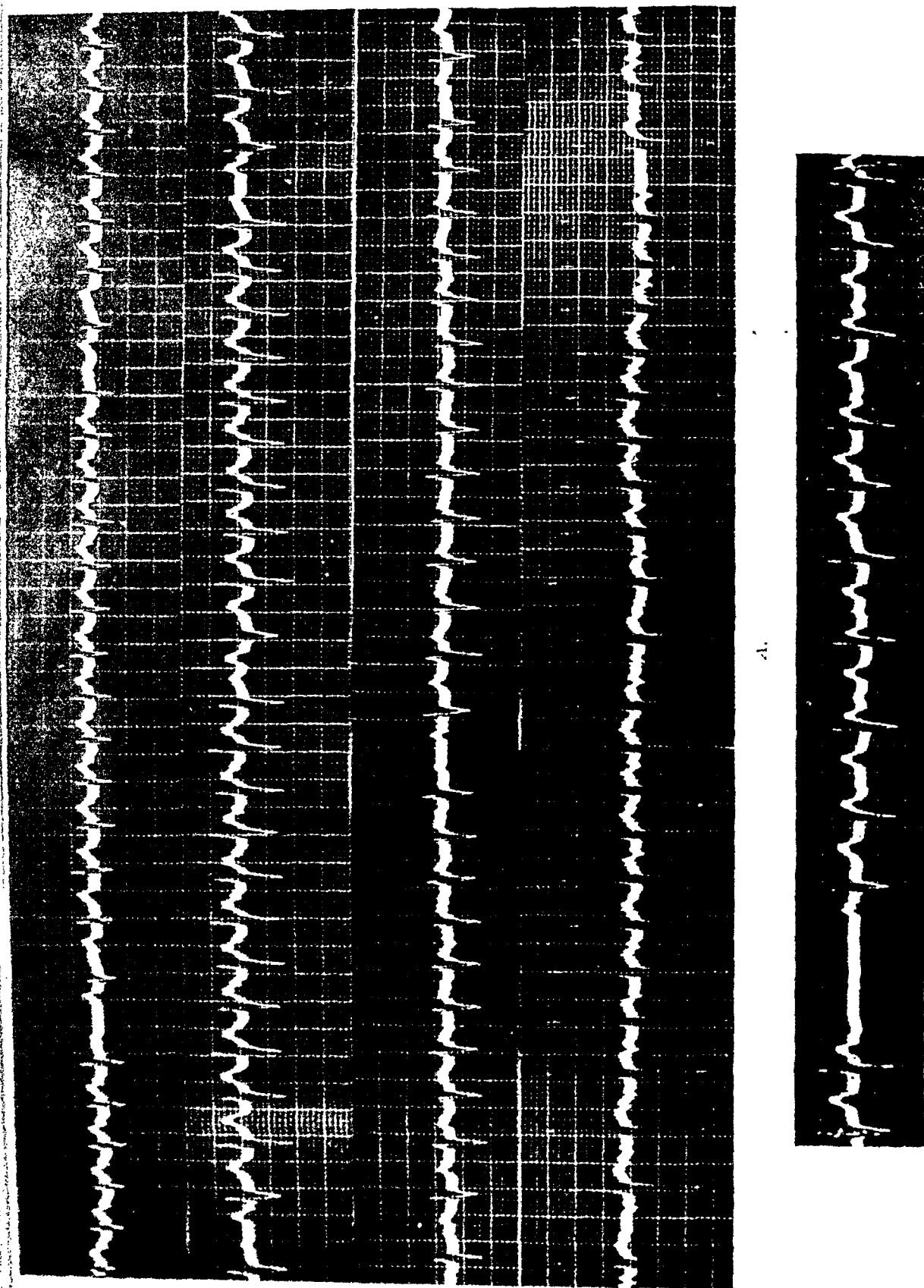


Fig. 3.—Case 2. A, November, 1945. Three standard leads and Lead IV F. B, Jan. 15, 1946. Lead II. Paroxysmal auricular tachycardia and A-V block, interrupted by normal sinus beats.



Fig. 4.—Case 2. Jan. 28, 1946. Normal sinus rhythm.

and the simultaneous administration of quinidine to restore the rhythm to normal. In the other patient, many trials of therapy with these methods were unsuccessful. In addition, he received potassium salts orally and prostigmine parenterally with a similar lack of response. On only one occasion, for a short period, was it possible to obtain a normal sinus rhythm by use of quinidine. This could not be repeated subsequently. A-V block was produced by digitalis in both patients.

There was no clinical evidence of heart disease in these patients. It is not known if the injury mentioned in Case 2 precipitated the tachycardia. Repeated physical examination by a number of observers failed to reveal any evidence of cardiac disease. In addition, x-ray and fluoroscopic study and electrocardiograms did not reveal any evidence of heart disease. The persistence of the tachycardia and the refractoriness to therapy are similar to the course in paroxysmal auricular tachycardia with A-V block. Lenhartz and Samet⁶ described a patient who had auricular tachycardia with A-V block who had recurrent attacks lasting up to ninety-four days. A patient reported by Maddox⁷ had auricular tachycardia which lasted sixty-nine days and was still present on the last examination. Levine⁸ mentioned a patient who had a chronic auricular tachycardia, with intermittent A-V block, which lasted for a period of nineteen years. This patient was alive at 72 years of age and was reported to have been ambulatory and without congestive failure during all that time.

The electrocardiograms in these patients bore a superficial resemblance to those of patients with paroxysmal auricular tachycardia with A-V block. The irregularity, however, was due to frequent termination of the paroxysms. In

the first patient each paroxysm was preceded by a normal sinus beat. In the second patient, normal sinus beats between the short paroxysms occurred only when A-V block was produced by digitalis (Fig. 3, B).

SUMMARY

1. Two patients with a chronic auricular tachycardia which consisted of short recurrent attacks of paroxysmal auricular tachycardia are reported on.
2. The condition was refractory to ordinary therapy.
3. In one of the two patients it was possible to revert the rhythm to a normal sinus rhythm by full digitalization followed by the administration of quinidine.
4. In the other patient, the arrhythmia persisted although the ventricular rate could be partially controlled by digitalis.

The author expresses his appreciation to Dr. Louis Wolff, of Boston, Mass., for his advice in the management of these patients and for his criticism of the manuscript.

REFERENCES

1. Barker, P. S., Johnston, F. D., and Wilson, F. J.: Auricular Paroxysmal Tachycardia With Alternation of Cycle Length, *AM. HEART J.* 25:799, 1943.
2. Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia With Auriculo-Ventricular Block, *AM. HEART J.* 25:765, 1943.
3. Decherd, G. M., Jr., Herrman, G. R., and Schwab, E. H.: Paroxysmal Supraventricular Tachycardia With A-V Block, *AM. HEART J.* 26:446, 1943.
4. Fine, M. J., and Miller, R.: Orthostatic Paroxysmal Auricular Tachycardia With Unusual Response to Change of Posture, *AM. HEART J.* 20:366, 1940.
5. Miller, R., and Perelman, J. S.: Chronic Auricular Tachycardia With Unusual Response To Change in Posture, *AM. HEART J.* 29:555, 1945.
6. Lenhartz, H., and Samet, B.: Quoted by Barker and co-workers.²
7. Maddox, K.: Auricular Paroxysmal Tachycardia (Possibly Nontopic) With Variable Auriculoventricular Conduction Time, *AM. HEART J.* 14:183, 1937.
8. Levine, S. A.: *Clinical Heart Disease*, ed. 3, Philadelphia, 1945, W. B. Saunders Co., Fig. 28, p. 320.

SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNG SIMULATING ORGANIC HEART DISEASE

EDWARD S. MCCABE, M.D.*
BALTIMORE, MD.

IN 1879, Laennec¹ gave the first accurate description of the pathologic anatomy of interstitial emphysema. Müller² in 1888 noticed fine, bubbling crepitations occurring synchronously with the heart beat as an early sign of mediastinal emphysema. The diagnosis, however, was only made clinically when air was discovered in the subcutaneous tissues, especially those of the neck, and when trauma or violent effort appeared in the history. Lister³ reported a single case and described a "pericardial knock," which he thought was due to partial obstruction of the pulmonary artery by tension or distortion caused by displacement of the lung.

It remained for Hamman^{4,5} to clarify this condition as a clinical entity and bring out the fact that spontaneous development of the lesion is frequent. Hamman stressed: (a) that no effort need be associated with its onset; (b) that radiation of the pain may simulate angina or coronary occlusion; (c) that there are usually no constitutional symptoms; (d) that a crunching, bubbling, crepitant, clicking, or popping sound may be heard over the heart with each contraction and that this sound is more marked after forced expiration (Hamman's sign); (e) that the area of cardiac dullness is diminished; (f) that pneumothorax may occur, usually on the left; (g) that roentgenogram may demonstrate air in the anterior mediastinum or subpleurally; and finally, (h) that the emphysema may follow the fascial planes and present itself peripherally.

As to pathogenesis, Macklin's⁶ work is of great interest. This author postulated that in these cases there is an inherent weakness in the alveolar wall, probably near its origin from the bronchiole. This wall ruptures and the escaped air infiltrates into the connective tissue travelling along the fascial planes toward the mediastinum or toward the visceral pleura. Which phase plays the more prominent role would seem to be determined by the pressure gradient existing within the alveolus at the time of rupture. Macklin⁷ has demonstrated experimentally that air tends to travel toward the mediastinum along the sheaths of the arteries, and often there are continuous channels from the peripheral alveoli to the hilus. The interstitial tissue about the bronchi contains no air. Having reached the hilus, air collects in bubbles along the borders of the mediastinum and about the heart vessels, infiltrating the tissues lying between

*From the Department of Medicine, Mercy Hospital, and the University of Maryland School of Medicine, Baltimore.

Received for publication Jan. 3, 1947.

the heart and the anterior chest wall. This distention of the mediastinum often causes pain of an extreme degree, with radiation similar to that of angina pectoris. It may give an alarming feeling of substernal pressure or, at times, a pleuritic pain made worse by deep breathing or coughing. Swallowing or turning the head may intensify the pain. The air may be trapped in the mediastinum and gradually absorbed, or it may burrow to the surface and appear above the clavicles, spreading up the neck and over the front of the chest. It also may go down posteriorly below the diaphragm into the retroperitoneal tissues.

Miller⁸ stated that six of eight cases of spontaneous interstitial emphysema that he has seen in three years had a complicating pneumothorax on the left side. Hamman's⁵ series shows two out of seven cases with left pneumothorax as a complication. Macklin⁷ has demonstrated that it is easy to have air escape from the mediastinum into the pleural space with an intact visceral pleura, but that the reverse is not possible. The probability still exists that air may travel along the interstitial bands of the lung to the pleura and form a subpleural bleb which may rupture. It seems more likely, however, in view of the experimental work, that air reaches the pleural cavity mainly through the mediastinum. The resulting pneumothorax may be of the tension type.

Symptoms and signs suggesting intrapericardial pressure may appear if the air pressure reaches the level of venous and intra-auricular pressure and impedes the filling of the auricles. The predilection for left pneumothorax as a complication may be due to the fact that the heart is anchored, as it were, by the cavae and the stress from the heart beat would be against the left mediastinal wall.

It is conceivable that an element of functional coronary insufficiency could arise and tend to obscure the diagnosis. Unfortunately, electrocardiograms were not taken in many of the reported cases and thus it is not possible to obtain a true incidence of electrocardiographic changes. Clinically, Hamman⁵ had three cases that simulated coronary occlusion. Wolferth and Wood⁹ and Scott¹⁰ reported several cases with anginal type pain. Lintz¹¹ points out that pericarditis, dissecting aneurysm, pulmonary infarct, mediastinitis, and intercostal neuritis, as well as angina pectoris and coronary occlusion, must be considered in the differential diagnosis. In Miller's⁸ cases with electrocardiograms recorded, the significant changes were flattened T wave in Lead I, with elevated S-T segments and inverted T waves in Leads II and III. These cases, however, were complicated by pneumothorax. Hamman⁵ had two cases in which electrocardiograms were taken. The findings were low voltage in all leads, especially in Lead I, and inversion of T wave in Lead II. Hamman reported a single case with inverted T waves in all three limb leads, with return to normal in ten days.

If the theoretical mechanism described in the preceding material is correct, then interstitial emphysema would give rise to right heart stasis from compression of the venous network in the lung proper and, secondarily, of the cardiac thebesian veins and the coronary sinus. Fisher¹² reported a fatal case in a child, and the findings were dilatation of the right ventricle and auricle with the pulmonary vessels compressed. Although the reason is obscure, according to McGuire and Bean,¹³ the subpleural bullae tend to develop between the parietal pleura and the pericardium. Thus, air acting as an insulator is probably re-

sponsible for the low voltage in the electrocardiograms and it may be of diagnostic value to measure the difference in voltage between an electrocardiogram taken in the supine position and one in a sitting position with some forward inclination. Fagin and Schwab¹⁴ in a recent review noted electrocardiographic changes of a significant nature in 25 per cent of reported cases. Their article includes a follow-up as regards spontaneous interstitial emphysema; approximately 20 per cent of the known cases were found to have suffered recurrences. One in particular required a therapeutic pneumothorax to promote healing. Fagin and Schwab pointed out that prognosis is excellent, except in infancy.

CASE REPORT

The patient was a 27-year-old white man, who was admitted to Mercy Hospital on June 24, 1946, with a chief complaint of pain in the left shoulder. He was apparently well until 1:00 P.M. on June 24, 1946, when he was seized by a sharp pain in his left shoulder after lifting a case of milk bottles shoulder high. This was one of his daily tasks. He stopped for lunch and while eating, the pain radiated down the left side of his chest to the precordial area. He lost his appetite and decided to lie down awhile in order to ease the pain. When it did not improve, a local

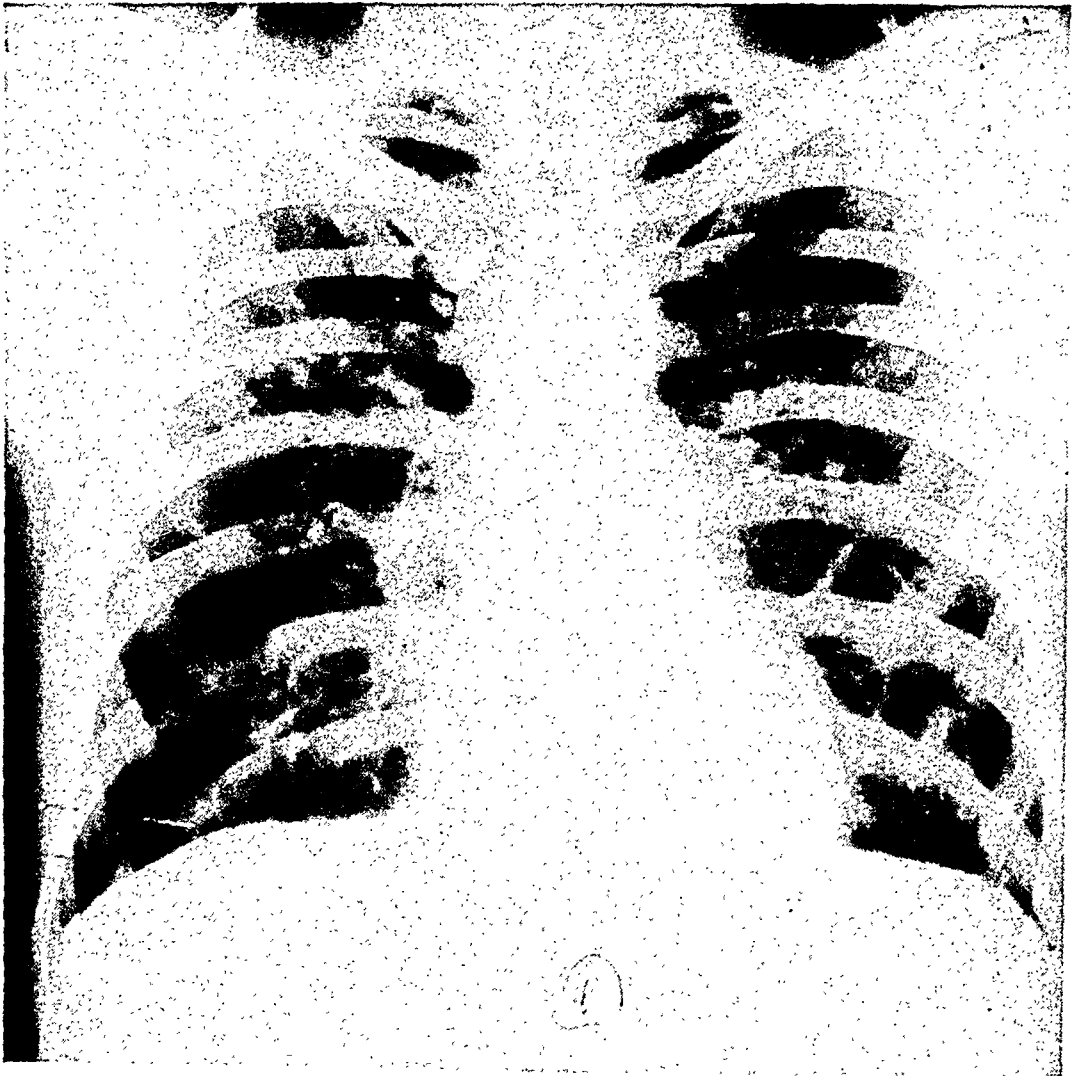


Fig. 1.—There are numerous radiolucent areas (emphysematous blebs) in the lower third of the left lung field.

physician was called who made a presumptive diagnosis of coronary occlusion and arranged for his admission to the hospital.

Systemic review was essentially negative. The past medical history revealed the usual childhood diseases and a few minor injuries, but no serious illnesses. In 1942, however, the patient was turned down by the Armed Forces because of shadows in his lung. In 1945, he had a chest x-ray that was considered clear by the Health Department. Social history and family history were not significant.

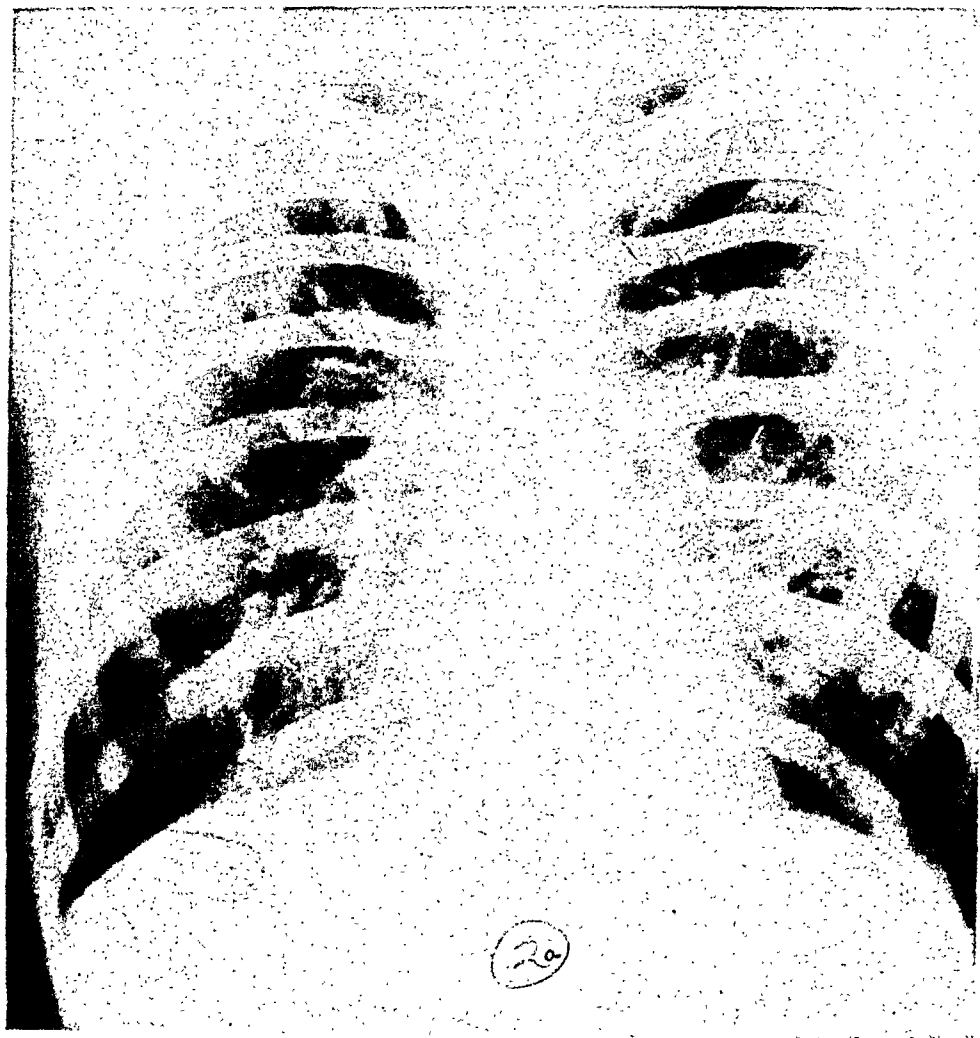


Fig. 2.—*a*, Anteroposterior view shows shift upward in air spaces, suggesting air is free. *b*, Emphysematous areas extending toward hilar region are seen in oblique view.

Physical examination revealed a husky white man in apparent pain. The temperature was 100° F.; pulse, 102; and respirations, 20 per minute. There was moderate dyspnea but no orthopnea. Examination of the eyes showed round, regular, and equal pupils which reacted to light and accommodation. Extraocular movements were normal. Eyegrounds revealed no abnormalities. There was slight hypertrophy of the right tonsil and an injected pharynx. Trachea was in the midline. There was no subcutaneous crepitation. Some cervical adenopathy was found. Thorax was symmetrical. There was a slight respiratory lag on the left, but expansion was good on both sides. Hyper-resonant percussion note on the left obliterated the area of cardiac

dullness at the apex. Breath sounds were diminished on the left, but a few crepitations were present. No heart murmurs were heard. There was rigidity in the epigastrium, probably voluntary; the liver and spleen were not felt. No costovertebral tenderness was elicited. Extremities were negative. Neurological examination was negative.

On June 24, hemoglobin was 16.8 Gm.; erythrocyte count, 7,340,000; and leucocyte count, 24,650, with 91 per cent polymorphonuclear leucocytes, 8 per cent lymphocytes, and 1 per cent eosinophils. Next day, hemoglobin was 16.2 Gm.; erythrocyte count, 5,070,000; and leucocyte



Fig. 2, b.—For legend see opposite page.

count, 12,200, with 69 per cent polymorphonuclear cells. Urinalysis was negative. Cephalin flocculation test was negative in twenty-four hours; 3 plus in forty-eight hours. Prothrombin time was 20 seconds undiluted, and 83 seconds diluted (12.5 per cent). Sedimentation rate corrected was 13 mm. in one hour. Bromsulfalein test was normal. On June 28, hemoglobin was 14.3 Gm.; erythrocyte count, 4,750,000; and leucocyte count, 6,850, with 61 per cent polymorphonuclear cells.

An x-ray of the chest (Fig. 1), on June 25, showed numerous radiolucent areas in the lower third of the left lung field, which had the appearance of emphysematous blebs. The lungs were

otherwise clear, except for fibrous tissue changes in the right axillary region. Heart and aorta were normal. On June 27 (Fig. 2, a and b), x-ray films showed that the emphysematous changes extended from the hilum outward and downward. There had been some shift of the air spaces upward from the diaphragm, suggesting that the air was free. On July 6 (Fig. 3), subpleural blebs were no longer seen in the left chest.

On June 26, venous pressure was 115 mm. of water. The arm-to-lung circulation time (ether) was 10 seconds. The arm-to-tongue time (with magnesium sulfate) was 14 seconds. The vital capacity was 4.6 liters.

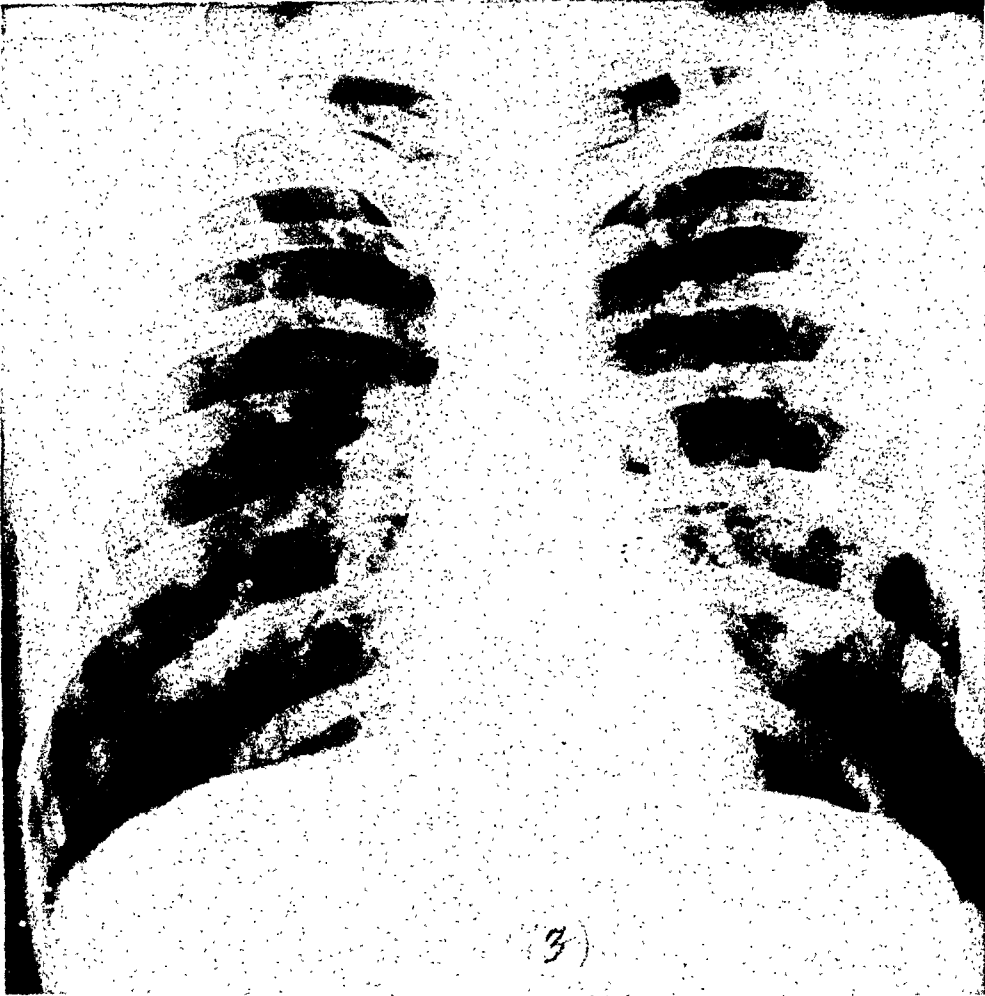


Fig. 3.—Subpleural blebs are no longer seen in left chest.

An electrocardiogram (Fig. 4), taken on June 24, showed sinus arrhythmia, tachycardia, and elevated S-T segments in Leads I, II, and IV. On June 25 (Fig. 5), there was accentuation of S-T segment elevation in Leads I, II, and IV, with an inverted T in Lead III. On June 27 (Fig. 6), the S-T segments were not elevated as much and the T wave was isoelectric in Lead III. On June 29, there was a sinus bradycardia (rate 60 per minute), and the T wave in Lead III was beginning to become upright. On July 2 (Fig. 7), S-T segment changes were within normal limits and T wave was upright and measured 0.2 millivolt.

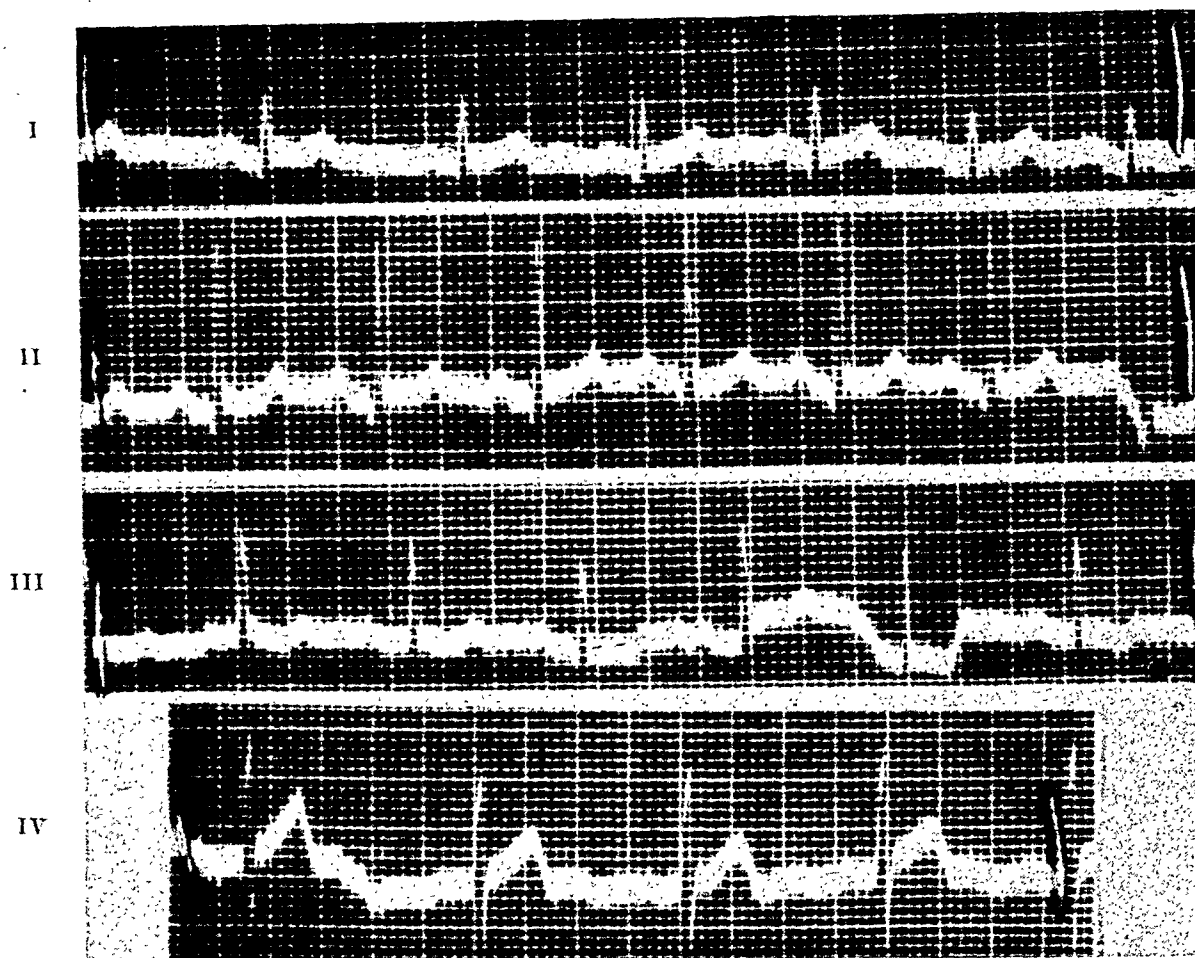


Fig. 4.—June 24, 1946. There is some elevation of S-T segments in Leads I and II.

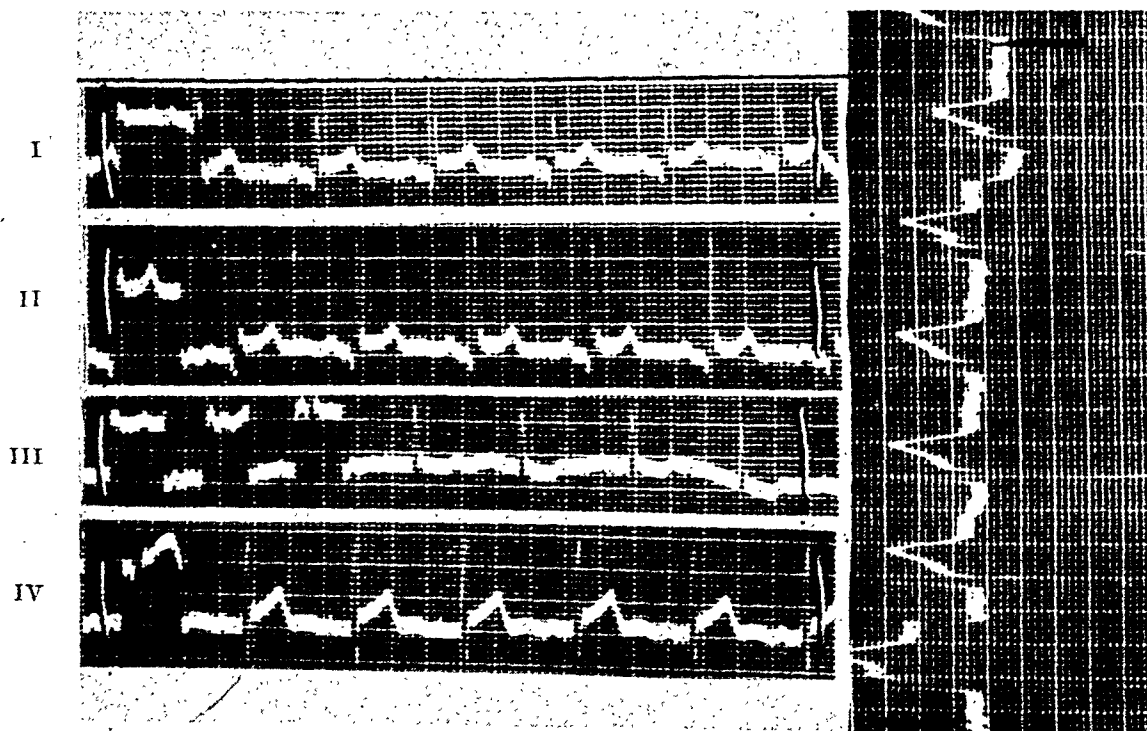


Fig. 5.—June 25, 1946. S-T segment elevation is more marked in Leads I and II.

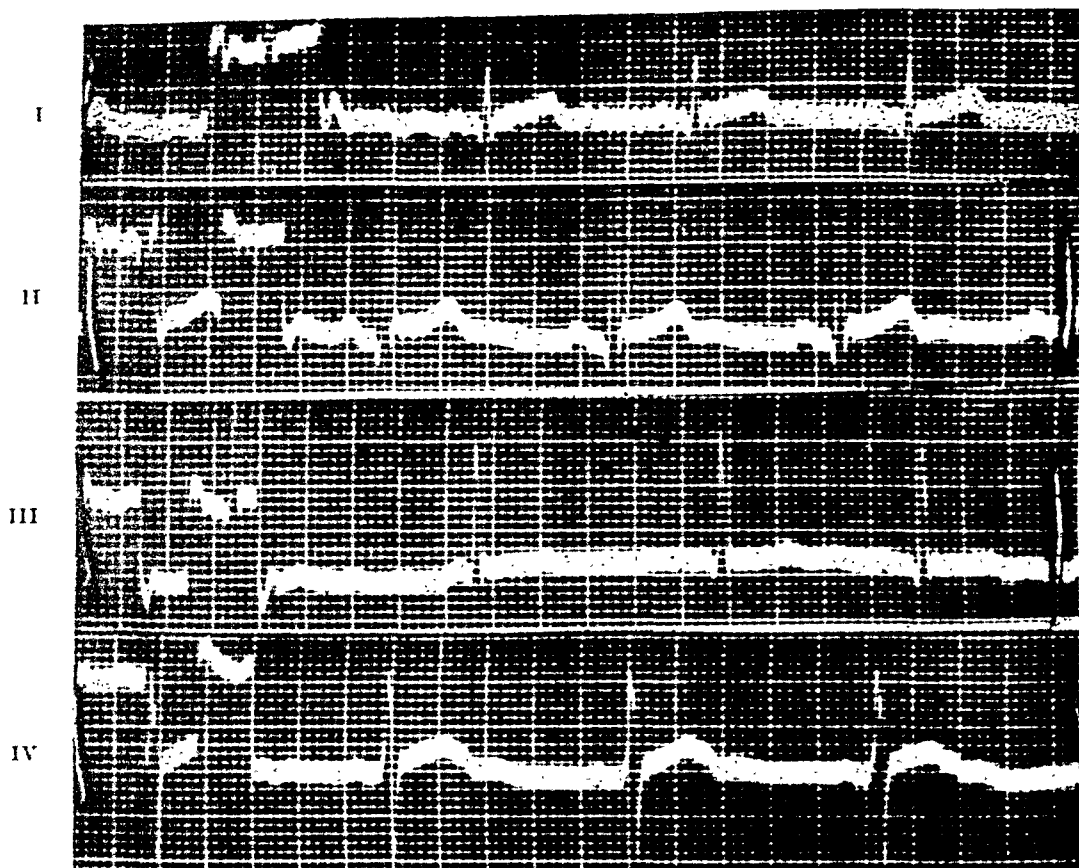


Fig. 6.—June 27, 1946. T waves are diphasic or isoelectric in Lead III, with S-T segments returning to base line in Leads I and II.



Fig. 7.—July 2, 1946. T wave upright in Lead III. Normal tracing.

DISCUSSION

It is postulated that all degrees of spontaneous interstitial emphysema exist and that the case herein presented was moderate in degree. This patient, a young man, was seen in what was described as an attack of coronary occlusion. The pain was severe enough to require morphine to relieve it. On admission he had a tachycardia with a rate of 102 per minute, a blood pressure of 130/90, moderate dyspnea with mouth breathing, and a very dry tongue. Heart sounds were not heard in the supine position, but were heard in the sitting position; crepitant râles were heard at the left base and were more pronounced during systole and during expiration. The area of relative cardiac dullness was replaced by an area of hyper-resonance. The muscles overlying the epigastric area were tense. An electrocardiogram taken at that time showed slight elevation of S-T segment in Lead I and depression in Lead III. There was leucocytosis, 24,600 with a right shift. Sedimentation rate was 13 mm. corrected. Because of the atypical picture, a chest x-ray was taken and this showed subpleural bullae at junction of parietal pleura and pericardium. Electrocardiogram the next day revealed marked elevation of S-T segments in Leads I, II, and IV, with an inverted T wave in Lead III. X-ray films of the lungs, including an oblique, show a shifting air pattern, although no evidence of pneumothorax or air in mediastinum could be seen.

Considering the fact that his pain was only present intermittently for two days, last showing up in the right shoulder, and that no subcutaneous emphysema could be demonstrated, it is thought the air that escaped into the mediastinum was minimal and in such a location as to remain confined. It was thought quite probable that the initial rent in the alveolar wall would close over early under conservative treatment and hence the air in mediastinum would be reabsorbed rapidly. Then, too, the pains could be due to simple dissection of the interstitial tissues or to functional coronary insufficiency, since venous outflow was impaired.

In four days his leucocyte count had returned to normal, blood pressure was 110/70, and pulse, 60 per minute. The electrocardiogram and prothrombin time were normal by the seventh day. The former showed S-T segment elevations in Leads I, II, and IV within normal limits and an upright T wave in Lead III of 0.2 millivolt. The second electrocardiogram reported would be compatible with pericarditis or anterolateral myocardial infarction. Prothrombin time on admission was 20 seconds undiluted, 75 seconds diluted (12.5 per cent). This is in line with Brambel's¹⁵ theory that the amount of prothrombin itself is relatively constant and that the proportion of activators to inhibitors varies ordinarily. Here it would seem that there was a diminished amount of inhibitors formed or an increased amount of activators liberated. The interstitial air would impair oxygen diffusion and diminish the activity of the reticulo-endothelial system in the lung which probably elaborates the inhibitors. Hence, with resorption the prothrombin time returns to normal. It is of interest that neither the vital capacity nor the venous pressure appreciably changed during

the seven days. Circulation times, both arm-to-lung and arm-to-tongue, were slightly longer at the end of the week.

With a past medical history of having been rejected by the Armed Forces in 1942 for lung shadows, it may be that a residual weak area in the wall of an alveolus gave way or that with a transitory atelectasis of one alveolus the adjacent one would be overstretched and the wall would tear. According to Graham and associates,¹⁶ in a severe case prompt measures in instituting decompression of the mediastinum will result in the saving of a life. Whatever the mechanism of its occurrence, it is important to recognize the condition early, since with appropriate treatment, the prognosis is good.

SUMMARY

1. A case of spontaneous interstitial emphysema of the lung is presented and the probable mechanism is discussed.
2. Constitutional symptoms are minimal as a rule, but they vary with the amount of escaped air, as does the duration of the objective findings.
3. Serial roentgenograms are a definite aid in establishing the diagnosis.
4. Organic heart disease is simulated frequently and serial electrocardiograms are in order.
5. Pneumothorax, especially on the left, is a frequent complication.
6. Prognosis is excellent in the majority of cases, except in infancy.

The author wishes to express his appreciation of the stimulating and helpful criticism given by Dr. Maurice C. Pincoffs.

ADDENDUM

Since the preceding case report was prepared four additional cases have been seen on the wards of Mercy Hospital. These were evenly distributed as to sex and all were in the third decade of life. One male and one female had evidently recurrent attacks. The presenting complaint was a sharp pain, sudden in onset, and felt usually in left shoulder area, moderate dyspnea, tachycardia, and a peculiar crackling sound over the precordium. Three cases had a left pneumothorax with 10 to 20 per cent collapse of the upper left lobe. One in particular could not be seen on an anteroposterior roentgenogram, and it was only after a film was obtained in the left anterior oblique position that the 10 per cent collapse was seen. All four did show some air in the posterior mediastinum in the latter view. A positive Hamman's sign was present for from two to five days, but after the first few days it could be demonstrated only when certain positions were assumed. The initial electrocardiograms in the supine position showed low voltage in all leads, especially Lead I, and diphasic and flattened T waves in Leads II and III were observed in two patients. With the tracing taken in the upright position, the voltage of the QRS in Lead I was trebled. With resorption of air, the voltages did not change significantly with position and the T waves became upright. One patient, a 28-year-old white man, had an electrocardiogram that showed a wandering sinus pacemaker, and within five days the tracing shifted back to sinus rhythm. The patients were all treated conservatively and kept at bed rest until the air was absorbed. Then, an additional period of two weeks was advised with a gradual return to normal activity. After a minimum of six months, no case of recurrence has been found in follow-up study.

REFERENCES

1. Laennec, R. T. H.: *Traite de L'Auscultation Mediate*, Paris, 1879, Asselin et Cie.
2. Müller, F.: *Ueber Emphysem des Mediastinum*, *Klin. Wehnschr.* 25:25, 1888.
3. Lister, W. A.: Case of Pericardial Knock Associated With Spontaneous Pneumothorax, *Lancet* 1:1225, 1928.
4. Hamman, L.: Remarks on the Diagnosis of Coronary Occlusion, *Ann. Int. Med.* 8:417, 1934.
5. Hamman, L.: Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.* 66:1, 1939.
6. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels From Alveoli to Mediastinum: Clinical Implications, *Arch. Int. Med.* 64:913, 1939.
7. Macklin, C. C.: Pneumothorax With Massive Collapse From Experimental Overinflation of the Lung Substance, *Canad. M. A. J.* 36:414, 1937.
8. Miller, H.: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease, *Am. J. M. Sc.* 209:211, 1945.
9. Wolferth, C. C., and Wood, F. C.: Angina Pectoris, *M. Clin. North America*, 13:947, 1930.
10. Scott, A. M.: The Significance of the Anginal Syndrome in Acute Spontaneous Pneumomediastinum, *Lancet* 1:1327, 1937.
11. Lintz, R. M.: Spontaneous Mediastinal Emphysema, *Arch. Int. Med.* 71:256, 1943.
12. Fisher, J. H.: Spontaneous Pulmonic Interstitial and Mediastinal Emphysema in an Infant, *Canad. M. A. J.* 44:27, 1941.
13. McGuire, J., and Bean, W. B.: Spontaneous Interstitial Emphysema of the Lung, *Am. J. M. Sc.* 197:502, 1939.
14. Fagin, I. D., and Schwab, E. H.: Spontaneous Mediastinal Emphysema, *Ann. Int. Med.* 24:1052, 1946.
15. Brambel, C. E.: Personal communication to the author.
16. Graham, E. A., Singer, A., and Ballon, H. C.: *Surgical Diseases of the Chest*, Philadelphia, 1935, Lea & Febiger.

REACTIONS TO DECHOLIN IN CIRCULATION TIME DETERMINATION

JAMES K. NORMAN, M.D.*
FORT WORTH, TEXAS

IN 1931, Winternitz¹ and others introduced Decholin as a substance to be used in the determination of circulation time. It has been used extensively. Decholin† is the sodium salt of dehydrocholic acid, an oxidative product of cholic acid which is derived from natural bile acids. Each cubic centimeter of Decholin contains 20 per cent sodium dehydrocholate. The manufacturers² state that "Intravenous use should be undertaken cautiously with the usual observation of the patient and aseptic technique. The parenteral administration of this solution is contraindicated in the presence of bronchial asthma, allergic phenomena, mechanical biliary obstruction, or severe hepatitis."

The Decholin method is usually employed in the following manner: with the patient resting in the recumbent position, the skin of the antecubital space is prepared with alcohol. A vein in the antecubital space is selected and entered by means of an 18-gauge needle. Four cubic centimeters of Decholin are rapidly injected into the vein. The time from the beginning of the injection until the patient experiences a bitter taste is measured accurately with a stop watch. This is recorded as the arm-to-tongue circulation time.

The average time obtained in normal subjects with this method is 15 seconds. About 18 seconds is considered prolonged and pathologic. It reflects the blood flow from the arm vein to the right heart, through the lungs, left heart, and arterial system to the tongue. Because it is a subjective test and depends on cooperation of the patient its use is somewhat limited.

In my own personal experience in at least 1,000 such tests, the method has been satisfactory. No untoward effects were encountered until the reactions which are to be reported were observed. It is considered significant that the material which produced reactions in the first two patients was from the same supply of Decholin, while that administered to the third patient was from a different supply. Search of the literature has failed to reveal a report of any such reactions to Decholin. Lederle Laboratories³ state that they have encountered no similar reactions, nor have any been reported to them.

CASE HISTORIES

CASE 1.—E. M. was a retired white seaman, 74 years of age. He was admitted to the U. S. Marine Hospital, Stapleton, New York, on April 6, 1946, with the history of gradually increasing

From the Medical Department, U. S. Marine Hospital, Stapleton, New York, the Harris Clinic, Fort Worth, and the Harris Memorial Methodist Hospital, Fort Worth.

Received for publication Oct. 15, 1946.

*Former S. A. Surgeon. U. S. Public Health Service, now in the Department of Medicine, Harris Clinic, Fort Worth.

†Decholin is sold in this country by Lederle Laboratories, Inc., under the name of sodium dehydrocholate solution.

dyspnea for the last year and occasional swelling of the feet and ankles. For one week, prior to admission, he had a nonproductive cough and low-grade fever. He gave no history of allergy. Physical examination revealed a thin, emaciated, elderly white man, who appeared chronically ill. Blood pressure was 142/82. The temperature was 100.8° F., pulse, 96, and respirations, 20 per minute. The neck veins were not engorged. The chest was symmetrical. Bilateral expansion was equal. Resonance, fremitus, and breath sounds were normal. There were numerous râles in both bases, more marked on the right. The heart was not enlarged. The rhythm was regular. The sounds were of poor quality and a soft aortic systolic murmur was heard. The abdomen was flat. The liver was not enlarged. There was slight pitting edema of both feet and ankles.

Determination of the circulation time was performed in the usual manner. The first attempt, using the right antecubital vein, was not successful because about half of the testing material was extravasated into tissue outside the vein. The left arm was then used and a satisfactory test obtained. The arm-to-tongue circulation time was found to be 26 seconds. Electrocardiogram showed changes compatible with diffuse coronary artery disease, but there was no evidence of frank infarction. X-ray films of the chest showed no abnormalities of the lung fields and the heart was not enlarged. This patient was digitalized, given chemotherapy, and supportive treatment. He showed definite improvement. One week later the test for circulation time was again performed. The left antecubital vein was again used and the test performed in the usual manner. Within two minutes after the test the patient went into shock, with unconsciousness, rapid rate of pulse, and profuse sweating; the blood pressure was unobtainable. He was given 7½ grains of caffeine sodium benzoate and 5 minims of adrenalin. He responded in about one minute. About five minutes after the test it was noted that the right antecubital space, the site of the original extravasation of Decholin, was markedly edematous, reddened, and pruritic. Three days later, skin tests for sensitivity to Decholin were performed, using 0.1 c.c. of undiluted Decholin injected intradermally in the volar surface of the left forearm. This evoked a marked local response with redness, swelling, and itching. The same test on a control subject was negative. Two days later, the test was repeated on the patient, but this time he was premedicated with benadryl, 50 mg., about one hour prior to the test. Again, a marked local response was noted.

CASE 2.—P. W. was a white merchant seaman, 42 years of age. He had always been in good health until about one year before admission, when he had virus pneumonia. He gave no history of allergy. He was admitted to U. S. Marine Hospital, Stapleton, on May 2, 1946, with the complaint of nonproductive cough and dyspnea for one week. The day before admission, he developed fever which rose to 101° F., with occasional profuse sweating and substernal tightness.

Physical examination revealed a pale, fairly well-developed white male, who appeared to be ill. His temperature was 100.6° F., and respirations, 18 per minute. The throat was negative. The heart was not enlarged. The rhythm was regular and the sounds were of good quality. The heart rate was 96 per minute. The blood pressure was 124/76. No murmurs, thrills, or friction rubs were heard. Expansion of the chest was equal. Expiration was somewhat retarded bilaterally. There was normal resonance and fremitus. Coarse sticky râles were heard throughout both lungs. The liver was not enlarged. The neck veins were not engorged and there was no edema.

Because of the dyspnea, it was thought advisable to determine the circulation time. It was found to be 15 seconds. About one minute after the injection of Decholin the patient had a violent asthmatic attack, which was immediately relieved by 5 minims of adrenalin. He had no recurrence of such an attack. X-ray films of the chest and electrocardiogram were subsequently negative. He received treatment for asthmatic bronchitis and made an uneventful recovery.

CASE 3.—E. C., a 64 year-old white man, a bookkeeper, entered Harris Memorial Methodist Hospital, Fort Worth, on July 31, 1946, for hernioplasty. Medical consultation was requested because medium râles were heard in the right lung base. The patient stated that he had been feeling well and had no cough, fever, or dyspnea. He gave no history of allergy.

Examination revealed him to be a well-developed, well-nourished white man. He did not appear acutely or chronically ill. Positive physical findings were confined to chest and right inguinal region. The thorax was symmetrical. Bilateral expansion was equal. The breath sounds,

resonance, and fremitus were normal throughout the chest. In the right base numerous medium râles were heard which did not disappear on coughing. There were a few similar râles in the left base which did disappear on coughing. The heart was not enlarged. The point of maximum impulse was in the left fifth intercostal space in the mid-clavicular line. The heart rhythm was regular and the rate was 72 per minute. There were no thrills or friction rubs. There was a soft aortic systolic murmur heard in the second intercostal space, just to the right of the sternum. Blood pressure was 110/75. There was no engorgement of the veins of the neck. The liver was not enlarged and not tender. There was no edema. There was a large reducible right indirect inguinal hernia and hydrocele about the size of a lemon. Pulse, temperature, and respiration, two days prior to our examination, had been normal. X-ray films of the chest showed the heart to be of normal size, but the aorta was moderately widened and tortuous. In the region of the right hilus there was an area of patchy increased density which extended down to the right base. Electrocardiogram was negative.

Determination of circulation time was performed in the usual way with Decholin, and found to be 14 seconds. About five minutes after injection of the Decholin he developed a widespread, diffuse urticaria. He was immediately given 50 mg. of benadryl, and within ten minutes the pruritus disappeared, but the urticarial wheals remained for about forty minutes.

COMMENT

We are unable to adequately explain the reactions, but they were definitely of an allergic nature. None of these patients had a history of allergy; although Case 2 had asthmatic bronchitis at the time of the test. It seems unreasonable to assume that there was primary reaction to Decholin per se, unless foreign protein contaminants were present. We were unable to obtain a precipitate after heating a sample of Decholin following addition of acetic acid. The reaction in Case 1 was typically anaphylactoid in nature and may represent a combination of the drug with a haptene with subsequent sensitization. Damaschek⁴ put forth this idea as the possible explanation of certain drug reactions in the production of certain blood dyscrasias (agranulocytosis).

SUMMARY

1. The histories of three patients who suffered three different types of allergic or allergic-like reactions to Decholin, when used in circulation time determinations, are presented.

2. It is concluded that: (a) Decholin, as used in the determination of circulation time, is capable of producing allergic-like reactions. (b) No patient with a history of allergy should be subjected to the Decholin method of determining the circulation time. (c) By eliminating those patients with asthma, much of its value is lost. (d) Allergy or allergic-like reactions may occur in patients without history of allergy. (e) Patients may be sensitized to Decholin and at least potentially dangerous consequences may result.

REFERENCES

1. Winternitz, M., Deutsch, J., and Brull, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutemlaufszeit mittels Decholinjektion, *Med. Klin.* 27:986, 1931.
2. Brochure on Decholin published by Lederle Laboratories, Inc., 1944, New York.
3. Personal communication from Lederle Laboratories, Inc.; June, 1946, New York.
4. Damaschek, W.: *Oxford Monographs on Diagnosis and Treatment*: Oxford University Press, New York.

BACILLUS COLI ENDOCARDITIS

REVIEW OF THE LITERATURE WITH REPORT OF A CASE*

D. E. FLETCHER, PH.D.

LITTLE ROCK, ARK.

HARRIES and Burtenshaw¹ in 1937 reviewed the literature of endocarditis produced by the coliform bacillus. According to these writers, positive blood cultures for *Bacillus coli* before death and from the heart vegetation after death, together with Gram stains on histologic sections of the vegetation showing gram-negative bacilli in significant numbers, should be the criteria used in establishing a case of endocarditis as due to *Bacillus coli*. They emphasized the ease with which *Bacillus coli* contamination may occur at autopsy. This postulate is both reasonable and sound.

Harries and Burtenshaw, using this standard, accepted five cases from those reported in the literature and added a sixth case. Those included were as follows: Horder² in 1908 reported a case of endocarditis which occurred in a 12-year-old boy. The duration of the illness was four months. The pathologic findings at autopsy were a large, friable vegetation on the aortic valve, splenomegaly, embolic phenomena, and peritonitis. A pure culture of *Bacillus coli* was obtained from the vegetation. Dickar³ in 1932 reported two cases of acute bacterial endocarditis in elderly persons in which *Bacillus acidi lactici* was isolated by ante-mortem blood culture and gram-negative rods were demonstrated in the vegetation. The aortic valve was involved in both cases while the mitral and tricuspid valves were involved in only one. The brain in one case showed multiple infarcts which resulted from septic emboli. Duhig⁴ in 1933 reported one case of acute endocarditis in a 25-year-old woman. *Bacillus coli* was isolated by culture from the blood stream ante mortem and from the vegetation post mortem. The anterior cusp of the mitral valve was completely involved by a large vegetation which extended on to the left atrial wall. The posterior cusp of the mitral valve and the remaining heart valves were not damaged. The following year (1934) Crawford and Cruickshank⁵ reported a case of acute endocarditis in a woman, 43 years of age, in which *Bacillus acidi lactici* were isolated from the blood stream before death and from the vegetation on the mitral valve and from the spleen at autopsy. The case of endocarditis studied by Harries and Burtenshaw¹ in 1937 occurred in an 18-year-old girl. Both cusps of

From the University of Arkansas School of Medicine, Department of Pathology.

Received for publication Sept. 11, 1946.

*Research paper No. 846, Journal Series, University of Arkansas.

the mitral valve, the attached chordae tendineae, and the auricular wall were involved by a large, deep red, friable vegetation. They cultured gram-negative bacilli from this vegetation. Clumps of short and coccoidal gram-negative rods were demonstrated in the fibrin thrombus on the mitral valve, and in the infarcts in the kidneys. Repeated ante-mortem blood cultures were negative.

Several cases of bacterial endocarditis in which *Bacillus coli* was assumed to be the etiological agent are present in the literature. However, due to either incomplete or inaccessible data they cannot reasonably be accepted as bacteriologically substantiated. They are as follows: Dickar³ in 1932 referred to cases of *Bacillus coli* endocarditis reported by Lenhartz,⁶ Jacob,⁷ Jockmann,⁸ and Summa.⁹ The records of these cases, except that of Jacob, are obscure and the latter's study deals primarily with *Bacillus coli* septicemia. Norris¹⁰ in 1911, in his book on cardiac pathology, stated that in sixty-six cases of endocarditis in which cultures were obtained from the heart's blood and from the vegetations on the heart valves, nine were positive for *Bacillus coli communis*. Norris did not substantiate this statement with specific cases. Thayer¹¹ in 1926, in his monograph on bacterial endocarditis, mentioned "one or two cases" in which *Bacillus coli* was obtained from the vegetations. He also referred to one case of Harbetz¹² in which gram-negative rods were obtained at necropsy. Obviously, such statements do not constitute case reports and should be included in any study with reservation. Cowan¹³ in 1927, in his treatise on acute endocarditis, stated that *Bacillus coli* was the etiological agent in two out of his series of 430 cases. He did not give complete data on these two cases. Phipps¹⁴ in 1932 reported a series of forty-four cases of acute bacterial endocarditis in which positive blood cultures for *Bacillus coli* were obtained in five. No mention was made as to whether gram-negative organisms were present in the vegetations. The mitral valve was involved twice, the aortic and mitral valves together once, and all three valves once. Inasmuch as *Bacillus coli* septicemia is of frequent occurrence, positive cultures for *Bacillus coli*, regardless of whether they are taken from the circulating blood or directly from the vegetation, are of questionable significance unless gram-negative rods are demonstrated in histologic sections of the vegetation. Table I summarizes the data pertaining to the valvular involvement in *Bacillus coli* endocarditis.

Apparently no cases of *Bacillus coli* endocarditis have been reported since 1937. The writer is reporting a recent case of acute bacterial endocarditis from which three positive blood cultures for *Escherichia coli* were obtained during life, and at autopsy large colonies of gram-negative rods compatible with *Escherichia coli* were demonstrated in multiple histologic sections from the vegetation on the mitral valve, from infarcts in the spleen and kidneys, and from thrombi in the common iliac arteries.

CASE REPORT

M. D., a white woman 30 years of age, was admitted to the University Hospital on Nov. 11, 1945, in shock. She had been hospitalized and treated for "strep throat, pneumonia, and blood poisoning" in July, 1945. A curettage was performed on Sept. 18, 1945, in an attempt to correct excessive vaginal bleeding. On Sept. 2, 1945, the patient was operated upon for a tubal

TABLE I. VALVULAR INVOLVEMENT IN PROVEN CASES OF BACILLUS COLI ENDOCARDITIS

AUTHOR	YEAR REPORTED	NO. OF CASES	VALVES INVOLVED			
			MITRAL	AORTIC	TRICUSPID	PULMONARY
Horder ²	1908	1		Aortic		
Dickar ³	1932	2	Mitral	Aortic Aortic	Tricuspid	
Phipps ¹⁴	1932	5	Mitral Mitral Mitral Mitral	Aortic Aortic	Tricuspid Tricuspid	
Duhig ⁴	1933	1	Mitral			
Crawford and Cruickshank ⁵	1934	1	Mitral			
Harries and Burtenshaw ¹	1937	1	Mitral			
Fletcher	1946	1	Mitral			
Total		12	9	5	3	0

pregnancy. The wound failed to heal. On Nov. 4, 1945, the patient began to vomit and to have rigors. The vomiting and rigors increased in severity, her condition became critical, and she was brought to the University Hospital.

On admission, the temperature by axilla was 103° F.; pulse, 148 per minute; respiration, 40; and blood pressure, 76/44. The abdomen was tender to palpation and slight muscle guard was evident. A draining sinus was present in the operative scar in the mid-lower abdominal wall. The liver was enlarged to percussion. The lungs were normal. The heart was normal in size, the rhythm was regular, the rate was rapid. The quality of the heart sounds was good and no murmurs were detected. Decubitus ulcers were present in the sacral region.

Laboratory studies showed a negative urinalysis, hemoglobin, 6 Gm., red blood cell count of 2,750,000, and a white blood cell count of 23,150, with 72 per cent polymorphonuclear leucocytes. The differential count showed a slight shift to the left. The Wassermann examination was negative. A blood culture taken on admission was positive for *Escherichia coli*.

The patient remained in the hospital sixteen days during which time her condition remained critical. She was irrational, had urinary and fecal incontinence, marked edema of the extremities, repeated rigors, clinical signs of meningitis, labored respirations, and increasing abdominal distention. Her skin had a café-au-lait pallor and petechiae appeared over the face and extremities. The axillary temperature fluctuated between 99° and 106° F., the pulse between 100 and 160, respiration between 20 and 50 per minute, and the blood pressure varied between 83/42 and 108/56. The specific gravity of the urine varied between 1.003 and 1.014 and the nonprotein nitrogen ranged between 50 and 112 mg. per cent. The plasma protein varied between 4.1 and 4.4 grams. The blood chlorides were 480 mg. per cent. Hemoglobin values varied from 6 to 11.75 grams. The total red blood cell count showed variations from 1,750,000 to 4,030,000 with transfusions, and the white blood cell count, 16,750 to 59,000. Blood cultures taken on Nov. 11, 16, and 25 were positive for *Escherichia coli*.

Autopsy Findings.—The autopsy was performed six hours after death. Only the pertinent findings are given. The heart weighed 335 grams. The ventricles appeared slightly dilated. The myocardium was red-brown in color and soft in consistency. A large grayish-red, rather

firm vegetation measuring 3 cm. in diameter was attached to the auricular surface of the anterior cusp of the mitral valve (Fig. 1). It practically occluded the atrioventricular orifice. It also involved both the ventricular and auricular walls adjacent to its base. The chordae tendineae of the anterior cusp were destroyed, whereas those of the posterior cusp were normal. Microscopically, the vegetation consisted of fibrin, red blood cells, polymorphonuclear leucocytes, and multiple colonies of gram-negative long and short rods and coccoidal forms (Fig. 2). The other valves were normal. The endocardium and myocardium adjacent to the vegetation were thickened and infiltrated by large numbers of polymorphonuclear leucocytes, red blood cells, and scattered mononuclear cells. The myocardium showed extensive necrosis in this region. The overlying epicardium was thickened and infiltrated by the same types of cells as were found in the myocardium. A mild diffuse scarring with scattered mononuclear cells was present throughout the remaining portions of the myocardium.

The lumina of both common iliac arteries were completely occluded by thrombi which extended from the aortic bifurcation 5 cm. distad. This did not have the characteristics of a riding embolus, but appeared to have resulted from the pelvic infection extending through the vessel walls. These thrombi consisted of fibrin, red blood cells, polymorphonuclear leucocytes, and gram-negative long and short rods and coccoidal forms. The vessel walls were thickened and diffusely infiltrated by large numbers of polymorphonuclear leucocytes and mononuclear cells.

The left pleural cavity contained 500 c.c. of straw colored fluid. The lungs were edematous, hemorrhagic, and indurated along their bases and posterior surfaces.

The peritoneal cavity contained 1,000 c.c. of a yellow, fibrinopurulent exudate. Multiple fibrous and fibrinous adhesions bound the greater omentum and intestines to the lower abdominal and plevic walls. The liver weighed 2,048 grams. It extended 5 cm. below the costal margin. The surfaces were covered with the exudate. The sinusoids were filled with red blood cells. The hepatic cells were swollen, pale staining, and granular appearing. Some showed vacuoles in their cytoplasm. There was a moderate lymphocytic infiltration about the portal triads.

The spleen weighed 340 grams. It was soft, friable, and deep red in color. Its surface was covered with the purulent exudate. The lower pole was completely necrotic. Multiple yellow infarcts containing colonies of gram-negative long and short rods and coccoidal forms were present throughout its substance.

The kidneys were soft and swollen. Their combined weight was 570 grams. The corticomedullary pattern was distorted by multiple yellow infarcts which also contained gram-negative long and short rods and coccoidal forms. Multiple petechiae were present in the mucosa of the pelvis. Many glomeruli showed small areas of degeneration. The epithelial cells of the tubules showed parenchymatous degeneration. Throughout the interstitial spaces were found collections of lymphocytes and polymorphonuclear leucocytes.

The uterus was slightly enlarged and the endometrium hemorrhagic. The large blood vessels in the tunica muscularis were hypertrophied. The basilar portion of the mucosa contained numerous tortuous glands embedded in a dense cellular matrix. Large pale-staining connective tissue cells suggestive of a decidual reaction were also present in the mucosa.

The fimbriated end, including a portion of the ampulla of the right Fallopian tube, was absent. The remaining portion of this tube measured 2 cm. in diameter and was hemorrhagic. The left Fallopian tube and both ovaries were obscured by numerous dense fibrous adhesions. The fimbriated end of the left tube protruded into the pelvic cavity as a swollen, bright red, puckering mass. The wall of both Fallopian tubes were infiltrated by mononuclear cells. The right tube also showed red blood cells, polymorphonuclear leucocytes, and decidual-like cells.

The pelvic colon and the walls of the cul-de-sac were bright red in color. Two sinus tracts with indurated walls connected the lumen of the rectum with the peritoneal cavity. The entire wall of the rectum adjacent to these sinuses was diffusely infiltrated by numerous small and large mononuclear cells and polymorphonuclear leucocytes.

The brain contained numerous recent and old areas of infarction and an occasional small abscess was seen. The cerebral cortex showed marked cellular degeneration. Glial proliferation and neuronphagia were conspicuous features. The meninges were diffusely infiltrated by a moderate number of mononuclear cells.



Fig. 1.—Interior of left auricle and left ventricle. A large, rather firm vegetation is attached to the auricular surface of the anterior cusp of the mitral valve.



Fig. 2.—Microscopic section through vegetation. Fibrin, red blood cells, polymorphonuclear leucocytes, and colonies of gram-negative long and short rods and coccoidal forms are seen.

Pathologic Diagnosis.—(History of curettage, tubal pregnancy, and salpingectomy with drainage from abdominal incision for nine weeks.) Sinus tracts connecting the lumen of the rectum with the peritoneal cavity. Fibropurulent peritonitis. Acute arteritis with thrombi in the common iliac arteries. Acute *Escherichia coli* endocarditis of the mitral valve. Edema and hemorrhage of the lungs bilaterally; a left hydrothorax of 500 cubic centimeters. Anasarca. Multiple infected infarcts in the kidneys, spleen, and brain. Acute cystitis; chronic pyelonephritis, bilaterally. Parenchymatous degeneration of the viscera. Splenomegaly. Decubitus ulcers over the sacrum and heels.

Bacteriologic Studies.—Blood cultures taken on three occasions showed gram-negative plump rods compatible with *Escherichia coli*. These organisms formed gray colonies on agar plates and colonies having a green sheen on eosin methylene blue plates. They formed acid and gas in Russel's tube and they were methyl red positive. Multiple histologic sections through the vegetation, through the infarcts in the spleen and kidneys, and through the thrombosed iliac arteries stained by the Gram's method showed groups of gram-negative long and short rods and coccoidal forms consistent with *Escherichia coli*.

DISCUSSION

Bacillus coli endocarditis corresponds both clinically and pathologically to acute endocarditis produced by streptococcus, pneumococcus, staphylococcus, and gonococcus. The clinical onset is sudden and is accompanied by chills, rigors, high fever, and marked sepsis. The course is rapid and usually terminates fatally within six to eight weeks. It is characterized by hemorrhagic and embolic phenomena. The vegetations are large, friable, and diffusely infiltrated with organisms. Multiple septic infarcts in the spleen, kidneys and brain are the common pathologic findings.

Acute bacterial endocarditis is usually produced only by organisms of high virulence.¹⁵ In view of the fact that the colon bacillus is considered low in pathogenic properties,¹⁶ it is interesting that all proven cases of *Bacillus coli* endocarditis have been of the acute type. This fact suggests that either the coliform bacillus, when it becomes pathogenic for man, has its virulence greatly increased or that an organism of low virulence may produce acute endocarditis. Furthermore, the type of vegetation which is formed on the heart valve by the colon bacillus is a proliferative growth and not the ulcerative lesion usually found in acute bacterial endocarditis. The pathologic findings in the heart, therefore, resemble those seen in subacute bacterial endocarditis. This clinico-pathologic discrepancy is of considerable interest.

Is the coliform bacillus capable of attacking an uninjured valve? This question is not discussed in the literature. It is generally believed, however, that only pathogenic organisms of high virulence will do this.¹⁵ In the present case there was no pathologic evidence to suggest previous damage to either the heart or its valves. Gram stains of the vegetation showed organisms morphologically compatible only with those cultured from the blood stream, which bacteriologic studies proved to be *Escherichia coli*. Furthermore, there was no suggestion of previous cardiac involvement in the clinical history. These facts suggest that *Escherichia coli* may attack and damage a healthy valve. It is also further evident that this organism may become virulent for man.

The mitral valve appears to be the valve most frequently involved in *Bacillus coli* endocarditis. Among the twelve cases reported which designate the valve involved, the mitral valve is implicated nine times, the aortic five times, and the tricuspid valve three times. The pulmonary valve has never been involved. Table I summarizes these data.

Although *Bacillus coli* septicemia is frequent, endocarditis as a sequel rarely occurs. However, when endocarditis does occur it usually follows some operative procedure.³ This fact is significant in the pathogenesis of this lesion. It is believed that the colon bacillus seldom passes through a healthy bowel wall. However, it has been shown experimentally that once the intestine is injured by either disease or trauma and a focus of infection established, a highly virulent strain of these organisms may develop.¹⁷ These bacilli may be capable of producing acute endocarditis should they enter the blood stream.

It is suggested that in the present case the wall of the rectum was injured during the operation for removal of the tubal pregnancy. Necrosis, ulceration, perforation, and peritonitis followed. The infection in the peritoneal cavity produced a virulent strain of *Escherichia coli* which invaded the blood stream. The marked sepsis, damage to the mitral valve, and development of the vegetation resulted. The valvular insufficiency thus produced gave rise to the murmurs which were heard for the first time six days after the patient entered the hospital. Two months expired between the time of the operation and the onset of the marked septicemia. During this interval the patient was bedfast and ample time was provided for necrosis and perforation of the rectum and the development of peritonitis. Sixteen days elapsed between the onset of septicemia and the appearance of the mitral murmur. This is the actual time required for the endocarditis to develop to the point where it could be clinically recognized. The remaining ten days until death were marked by infarction and hemorrhagic phenomena.

SUMMARY

The literature pertaining to *Bacillus coli* endocarditis is reviewed, summarized, and evaluated. An additional case is reported. The clinical manifestations of *Bacillus coli* endocarditis are those of an acute bacterial endocarditis. The vegetation produced on the heart valve is a proliferative rather than an ulcerative lesion. In this respect it resembles the lesion usually found in subacute bacterial endocarditis. It is significant that *Bacillus coli* endocarditis usually occurs as a postoperative complication rather than as a primary disease process. It is suggested that the coliform bacillus may attack a normal valve. The probable pathogenesis of the lesion in the present case is discussed and the clinical and pathologic findings are correlated.

REFERENCES

1. Harries, G. E., and Burtenshaw, J. M. L.: Acute Infective Endocarditis Due to Bacterium Coli, *Lancet* 2:803, 1937.
2. Horder, T. J.: Infective Endocarditis With an Analysis of 150 Cases and With Special Reference to the Chronic Form of the Disease, *Quart. J. Med.* 2:289, 1908-1909.

3. Dickar, L.: Acute Bacterial Endocarditis Due to *Bacterium Acidi Lactici*, *Arch. Int. Med.* 49:788, 1932.
4. Duhig, I. V.: Septicemia and Acute Infective Endocarditis Due to *Bacterium Coli*, *M. J. Australia* 1:435, 1933.
5. Crawford, A. M., and Cruickshank, R.: A Case of Infective Endocarditis Due to *Bacillus Coli*, *Glasgow M. J.* 22:21, 1934.
6. Lenhartz, H.: *Die septischen Erkrankungen*, Vienna, 1903, Alfred Hölder. (After Dickar.)
7. Jacob, L.: Ueber allgemeininfektion durch *Bacterium Coli Commune*, *Deutsches Arch. f. klin. Med.* 97:303, 1909. (After Dickar.)
8. Jockmann, G.: Ueber Endocarditis septica, *Klin. Wchnschr.* 49:436, 1912. (After Dickar.)
9. Summa; quoted by Kraus, F., and Burgsch, T.: *Spezille Pathologic und Therapie innerer Krank-Heiten*, vol. 2, Berlin, 1913, Urban & Schwarzenberg, pp. 1164. (After Dickar.)
10. Norris, G. W.: *Studies in Cardiac Pathology*, Philadelphia, 1911, W. B. Saunders Company, pp. 26.
11. Thayer, W. S.: *Studies in Bacterial (Infective) Endocarditis*, Johns Hopkins Hospital Reports, Vol. 22, 1926.
12. Harbetz, F.: *Studies ueber Endokarditis*, *Deutsche med. Wchnschr.* 25:121, 1899. (After Thayer.)
13. Cowan, J.: a. *Acute Endocarditis; A Clinical Study*, *Glasgow M. J.* 108:249, 1927.
b. *Acute Endocarditis; A Clinical Study*, *Glasgow M. J.* 108:338, 1927.
14. Phipps, C.: *Acute Bacterial Endocarditis*, *New England J. Med.* 207:768, 1932.
15. Libman, E., and Friedberg, C. K.: *Subacute Bacterial Endocarditis*, London-New York, 1941, Oxford University Press, pp. 59-76.
16. Zinsser, H., and Bayne-Jones, S.: *A Textbook of Bacteriology*, ed. 8, New York, 1939, D. Appleton-Century Company, Inc., pp. 492.
17. Medical Research Council: *A System of Bacteriology*, London, 1929, His Majesty's Stationery Office, Chapter 4.

ENDOCARDIAL POCKETS OF LEFT ATRIUM

H. K. HELLERSTEIN, M.D.

CLEVELAND, OHIO

THE object of this paper is to describe multiple endocardial pockets of the left atrium in a patient with chronic rheumatic heart disease with mitral insufficiency.

LITERATURE

The subject of endocardial pockets was excellently reviewed by Saphir in 1930 and 1933.^{1,2} Few additional reports have appeared in the American literature. Abbott reported the first of five known cases of pockets in the left atrium.³ She found an endocardial pocket in the thickened left atrium of a heart which was the seat of rheumatic mitral stenosis and which had a large patent foramen ovale. The concavity of the pocket pointed toward the left pulmonary vein. The patient, a 38-year-old white woman, had rheumatic fever at the age of 14 years and for ten years preceding death had been in cardiac decompensation. In the absence of histologic details, congenital cardiac malformation cannot be excluded.

Saphir¹ reported the second case of endocardial pockets of the left atrium in a heart which was the seat of chronic rheumatic mitral valvulitis with insufficiency. The patient was 6 years of age. In an area 2 cm. above the mitral valve, the atrial endocardium contained two pockets, 3 and 5 mm. in width. They were open toward the mitral valve. The surrounding portions of endocardium were grayish-white and thickened. Saphir considered them to be primarily inflammatory in origin and to be formed secondarily by regurgitation after the insufficiency of the mitral valve had been established.

The third and fourth cases of endocardial pockets of the left atrium were also presented by Saphir.² Clinical data were not included in this report. The third case resembled the second morphologically. In the fourth case, the pockets of the left atrium were secondary to a perforated fossa ovalis. Examination of the heart revealed an acute verrucous and ulcerating endocarditis of the mitral valve superimposed on a healed endocarditis. In the region of the fossa ovalis there was a round opening measuring about 8 mm. in diameter, the wall of which was thickened, firm, and slightly ragged. This opening had established a communication between the left and right atria. Between this opening and the posterior leaflet of the mitral valve there was one large somewhat horseshoe-

From the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio.

Received for publication Oct. 16, 1946.

shaped pocket and two smaller ones, the openings of all of which were directed toward the perforated fossa ovalis. The perforation of the fossa ovalis was the result of a mural ulcerative endocarditis in this region. Sections of the pockets revealed simple fibrosis and hyalinization but hardly any inflammatory cells or blood pigment. Saphir considered it likely that the pockets were caused by simple mechanical irritation brought about by the columns of blood and pressure of the blood circulating through the perforated fossa ovalis. This irritation first produced circumscribed endocardial thickenings and then the pockets.

Parsonnet and collaborators⁴ reported the fifth case in a 33-year-old white man with a massive left atrium secondary to rheumatic mitral insufficiency of twenty-five years' duration. The endocardium above the posterior cusp of the mitral valve was roughened and wrinkled. On the posterior wall of the left atrium there were two semilunar endocardial pockets consisting of fibrous thickening of mural endocardium with concavities pointing toward the pulmonary veins. Microscopic sections of the left atrium revealed healed and acute rheumatic auriculitis. However, no description of the endocardial pockets was presented.

CASE REPORT

L. F., a 48-year-old white woman, was admitted to Lakeside Hospital on March 14, 1946, with a chief complaint of shortness of breath. During the five months prior to admission the patient had developed progressive dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Edema of the lower extremities first appeared in February, 1946. This was the first episode of cardiac failure. The past medical history included the development of rachitic dorsal kyphoscoliosis at the age of 7 years. There was a questionable childhood history of rheumatic fever, with a definite residual apical systolic murmur.

On admission the patient was markedly cyanotic and dyspneic. The temperature was 36.7°C.; pulse, 88; respiratory rate, 20 per minute; and blood pressure, 130/90. There were present a caput quadratum and a marked deformity of the spine, consisting of a right dorsal scoliosis and kyphosis. Râles were heard at both lung bases. The left border of cardiac dullness was 3 cm. to the left of the midclavicular line in the fifth intercostal space. The heart rate and rhythm were normal. There was a harsh, high-pitched systolic murmur and a systolic thrill elicited best at the apex. Pitting edema of both lower extremities was present. The patient did not respond to digitalis and oxygen therapy and died on the third hospital day. The clinical diagnosis was cor pulmonale secondary to kyphoscoliosis.

Autopsy (9114) revealed chronic inactive rheumatic heart disease with profound mitral insufficiency, marked kyphoscoliosis with displacement and rotation of the heart, slight bronchopneumonia, and severe chronic passive hyperemia of the lungs, liver, spleen, and other viscera.

Eleven separate endocardial pockets were situated on the posterior wall of the left atrium (Fig. 1); ten were above the posterior commissure of the mitral valve and posterior mitral leaflet in an area 2.8 by 2.8 cm., and one was 0.6 cm. above the anterior commissure. One pocket rested partly on the interatrial septum at the inferior border of the fossa ovalis. The outline of the pockets was concave, with the concavity directed toward the apex of the heart. The pockets varied in depth from 0.2 to 0.5 cm. and from 0.5 to 1.8 cm. in their long axis, which was directed transversely, that is, roughly parallel to the valve ring. The projections forming the walls of the pockets were firm and gray. Their outer aspect was nodular, opaque, and finely wrinkled. The endocardium of the left atrium was thickened and its surface was wrinkled, dull, and opaque.

The heart weighed 329 grams. There was slight cor pulmonale and persistent ligamentum arteriosum. The pulmonic, aortic, and tricuspid valves were slightly thickened and opaque without fusion or shortening of the leaflets. The mitral valve was markedly thickened, opaque, and vascularized, particularly at the base of the leaflets. At the line of closure there were nu-

merous lamblian excrescences. There were thickening, retraction, and adhesions of the chordae tendineae. The anterior and posterior papillary muscles were hypertrophic and exhibited fibrosis of the tips.

Microscopic sections obtained according to the method of Gross, Antopol, and Sacks⁵ were stained with hematoxylin and eosin. In addition, serial sections of two pockets were made. Alternate fifth sections were stained for elastic and connective tissue with hematoxylin and eosin, and by the combined Weigert and van Gieson methods (Figs. 2 and 3).



Fig. 1.—Endocardial pockets on posterior wall of left atrium. Thickening and retraction of chordae tendineae; vascularity of base of anterior mitral leaflet in lower left corner.

The endocardial pockets were orderly arranged masses of smooth muscle cells and elastic and collagenous tissue. The whole pocket appeared to arise from the superficial portion of the endocardium; that is, from a subendothelial location. There was reduplication of the elastic fibers above and below the pockets and extension of the elastic lamellae from the endocardium into the pockets (Fig. 2). They split into laminae on both the inner and outer surfaces of the pockets and formed an elastic network for smooth muscle cells and collagenous tissue in the substance of the pockets. There was slight whorling of the elastic fibers at the tip; that is, the distal outermost part of the projection (Fig. 3). The smooth muscle fibers were oriented transversely and fanned out from the lateral attachments so that in the middle two-thirds of the pockets they extended from the free border to the line of attachment. On section, the fibers presented a honey-combed appearance with centrally placed nuclei and vacuolated or clear cytoplasm (Fig. 3). The muscle cells occurred usually as compact groups or bundles and occasionally as discrete fibers. In the vicinity, or at the border, of the muscle cells there was an irregular delicate network of elastic fibers, most of which surrounded the muscle cells. The dense, sparsely cellular collagenous connective tissue was disposed in transverse bundles at the base, and longitudinally in less well-marked bundles in the free portion. The base of the pocket was partly filled with collagen. There was no vascularity, cellular exudate, or pigmentation of the endocardial pockets or the surrounding region.

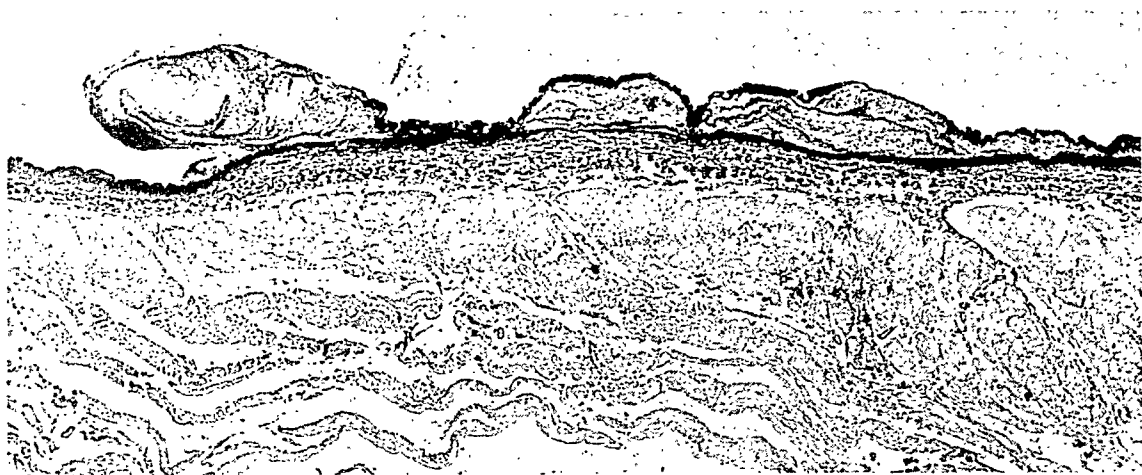


Fig. 2.—(Autopsy 9114). Endocardial pocket of left atrium and endocardial reduplications (Weigert and van Gieson $\times 30$).



Fig. 3.—(Autopsy 9114). Higher magnification of endocardial pocket. Whorling of elastic fibers at the tip; honeycombed appearance of transverse smooth muscle fibers (Weigert and van Gieson $\times 117$).

The mitral valve showed fibrous thickening with endocardial reduplications extending from the base to the line of closure. These were well vascularized with numerous capillaries and musculoclastic blood vessels and contained bundles of smooth muscle cells and occasionally foci of lymphocytes and plasma cells in the auricularis layer. The aortic and pulmonic valves were similarly but less severely involved. The endocardium of the left atrium was widened by numerous subendothelial plaques (endocardial reduplications) consisting of papillary masses of loosely arranged bundles of collagenous connective tissue and coarse bundles of elastic fibers. There were marked hypertrophy of the smooth muscle cells in the outer portion of the endocardium proper and irregular patchy and diffuse fibrosis of the endocardium. No Aschoff bodies were found.

DISCUSSION

Reported cases of endocardial pockets of the left atrium are rare.¹⁻⁴ Endocardial pockets of the left ventricle as a coincidental finding in cases of insufficiency of the aortic valve are relatively frequent in our experience and in that of others.^{1,2,6} Saphir reported one case of endocardial pockets in the right ventricle.² There was a perforation of the interventricular septum, and beneath the perforation, in the right ventricle, there was an endocardial pocket, the opening of which was directed toward the perforation. In the periphery of the pocket, several small areas of endocardial thickening could be distinguished. The perforation of the septum was probably the result of an old ulcerative mural endocarditis. Saphir considered this pocket to be an anatomic witness of the interchange of blood between the ventricles. No sections were taken from this pocket. Review of the literature revealed no cases of endocardial pockets of the right atrium.

Valvular deformity has been present in every reported case of endocardial pockets. The nomenclature proposed by Krasso⁷ designated diastolic pockets as those which opened toward the aorta and systolic pockets as those which opened toward the apex. Diastolic pockets were found in cases of aortic insufficiency and systolic pockets in cases of aortic stenosis and of mitral insufficiency. The pockets secondary to aortic valvular disease were located on the interventricular septum from 0.5 to 5.0 cm. below the aortic ring. The pockets of the left atrium were located from 2.0 to 3.0 cm. above the posterior mitral leaflet and in the region of the interatrial septum.

The endocardial pockets consisted of thickened endocardial folds and usually had a semilunar contour. They were composed of smooth muscle cells and elastic and collagenous tissue in orderly arrangement and arose from the superficial portion of the endocardium. Elastic lamellae extended from the endocardium into the pockets. No inflammatory reaction was present. The morphology of the left atrial pockets in the present case is similar to that described by Saphir¹ in his Cases 3 and 4, that is, systolic and diastolic endocardial pockets of the left ventricle in hearts with syphilitic involvement of the aortic valve. In Ingham and Henthorne's⁶ three cases of endocardial pockets of the left ventricle, resulting from subacute bacterial endocarditis superimposed on old rheumatic endocarditis, chronic rheumatic endocarditis, and calcareous aortic stenosis, respectively, the elastic tissue similarly formed laminae on both the inner and outer surface of the pockets and also provided a fine elastic meshwork for

the connective tissue structure. In one case bundles of normal heart muscle extended into the base of the pocket in a manner similar to the extension of muscle into the tricuspid valves of normal infants. Smooth muscle cells were not found in the pockets of any of the reported cases.

Three theories have been proposed to explain the origin of atrial and ventricular endocardial pockets: (1) purely mechanical, (2) primarily inflammatory and secondarily mechanical, and (3) congenital malformation. The chronic prolonged irritation of regurgitating blood is believed to result in simple circumscribed endocardial thickenings and endocardial pockets. Exemplary cases are those of syphilitic aortic valvular insufficiency in which there are endocardial pockets on the septal surface of the left ventricle with complete absence of local inflammatory reaction. Evidence for an inflammatory basis consists of the presence of small blood vessels, remnants of blood pigment, and inflammatory cells at the line of attachment of the pockets to the endocardium and occasionally extending into the pockets. In every such case, there was a coexistent valvular defect. The pockets are then formed secondarily by mechanical excavation of the regurgitating stream of blood. The possibility that the pockets are congenital anomalies cannot be excluded with certainty, although in every reported case there has been an associated valvular lesion, either rheumatic or syphilitic. Ingham and Henthorne⁶ state that there may be congenital folds of endocardium which require only the hemohydraulic factor of regurgitation resulting from insufficiency of the valves to form the pockets.

In the present case, endocardial pockets occurred in a heart which showed the stigmas of chronic rheumatic disease, that is, vascularization of the valves with thick-walled arteries, endocardial reduplication, and fibrosis of the valves and of the left atrial endocardium. The mitral valve was insufficient. In the absence of inflammation demonstrated by serial sectioning, it is logical to assume that the endocardial pockets were formed mechanically by the regurgitating blood stream. The endocardium in the region of the pockets was the seat of endocardial reduplication and thickening in this and other cases. The left atrial endocardial reduplications may be inflammatory or mechanical in origin. Endocardial reduplication, endocardial fibrosis, and hypertrophy of smooth muscle are suggestive of rheumatic disease. The absence of pathognomonic stigmas of rheumatic endocarditis (vascular penetration, cellular exudate, musculoelastic arteries, and Aschoff nodules) in the left atrium of the present case is not incompatible with an inflammatory origin of the endocardial reduplications. These stigmas in the left atrium may be absent in proved cases of rheumatic heart disease with mitral deformity.⁸

The possibility of a mechanical origin of endocardial reduplication and thickening of the left atrium of our case is suggested by the presence of similar noninflammatory lesions in localized regions of the interventricular septum subjacent to diseased aortic valves and by the absence of such lesions in cases without aortic valvular involvement.

Regardless of the origin of endocardial reduplication, in the final analysis the pockets are formed by the action of regurgitating blood which probably mechanically excavates the reduplicated endocardium with proliferation and

elastic transformation of connective tissue and metaplasia of subendothelial mesenchymal tissue into smooth muscle which later undergoes hypertrophy.

In this case and the cases reported by Parsonnet and co-workers⁴ and by Abbott³ the mitral lesion had existed forty-one, twenty-five, and twenty-four years, respectively. The significance of long duration of mitral insufficiency is problematic in view of the relative infrequency of pockets in long-standing cases of valvular heart disease. Furthermore, the patient reported by Saphir was only 6 years old. The chest deformity of our patient with rotation and displacement of the heart conceivably may have altered the dynamics of a regurgitating valve. This may have resulted in further traumatization of the posterior atrial endocardium and may have aided in the production of the lesions.

Saphir¹ believes that endocardial pockets cannot be regarded as manifestations of functional adaptation. In order for endocardial pockets to function effectively as valves, it would be necessary that the pockets be larger and sufficiently close to appose each other. The capacity of the pockets is small and probably of no functional importance. The significance of endocardial pockets, other than being a coincidental finding, is to indicate anatomic incompetence of a valve.

SUMMARY

A case which exhibited eleven endocardial pockets of the left atrium secondary to chronic rheumatic mitral insufficiency is presented.

The endocardial pockets consisted of thickened endocardial folds which usually had a semilunar contour. The concavity of the pockets was directed toward the apex of the heart. The pockets were composed of masses of smooth muscle cells and elastic and collagenous tissue in orderly arrangement and arose from the superficial portion of the endocardium. There was no vascularity, cellular exudate, or pigmentation of the endocardial pockets or surrounding endocardium.

Prolonged regurgitation of blood and the resulting pressure are the most significant factors in the development of endocardial pockets.

I am indebted to Dr. Howard T. Karsner and Dr. Simon Koletsky for their assistance in the preparation of the manuscript.

REFERENCES

1. Saphir, O.: Endocardial Pockets, *Am. J. Path.* 6:733, 1930.
2. Saphir, O.: Anatomic Evidence of Functional Disorders of the Heart, *Arch. Path.* 16:315, 1933.
3. Abbott, M. E.: Two Cases of Widely Patent Foramen Ovale, *Internat. Assoc. Med. Mus. Bull., Wash.* 5:129, 1915.
4. Parsonnet, A. E., Bernstein, A., and Martland, H. S.: Massive Left Auricle With Special Reference to Its Etiology and Mechanism. Report of a Case, *AM. HEART J.* 31:438, 1946.
5. Gross, L., Antopol, W., and Sacks, B.: A Standardized Procedure Suggested for Microscopic Studies on the Heart With Observations on Rheumatic Hearts, *Arch. Path.* 10:840, 1930.
6. Ingham, D. W., and Henthorne, J. C.: Endocardial Pockets, *Arch. Path.* 25:250, 1938.
7. Krasso, H.: a. Ueber atypische endocardiale Taschenbildungen bei Aorteninsuffizienz, *Frankfurt. Ztschr. f. Path.* 32:173, 1925.
b. Die pseudovalvulären Bildungen des parietalen Endokards bei Aortenklappenfehlern und ihre Bedeutung, *Frankfurt. Ztschr. f. Path.* 37:136, 1929.
8. Koletsky, S.: Microscopic Lesions of the Left Atrial Endocardium in Chronic Rheumatic Heart Disease, *AM. HEART J.* 29:739, 1945.

Abstracts and Reviews

Selected Abstracts

Pruche, A.: Electrocardiograms Obtained From Precordial Positions Defined by X-rays. Arch. d. mal. du coeur 39:323 (Oct.), 1946.

A system of bipolar precordial leads very similar to that introduced twenty years ago in Germany by Ackerman and associates is reintroduced (no reference is made to previous work). Under fluoroscopic control the beginning of the ascending aorta, the point of opposite pulsation, and the cardiac apex are marked on the chest. Electrocardiographic leads are recorded in a triangular fashion from these three points, similar to the method used for the recording of standard bipolar limb leads. A number of normal and abnormal patterns obtained by this method are presented and discussed.

HECHT.

Lian, C., and Minot, G.: Radio-Electrokymography. Arch. d. mal. du coeur 39:339 (Oct.), 1946.

The authors describe a technique by which the pulsations of the heart and great vessels may be transformed and amplified by a photoelectric cell which is mounted on a fluoroscopic screen. The pulsations may be recorded simultaneously with an electrocardiogram on sensitized paper. Four examples of pulsations of the left ventricular border and two of expansile pulsations of the aorta are presented. Beginning and ending of cardiac ejection thus may be clearly defined. An example of aortic insufficiency demonstrates abnormal pulsations of the left ventricle and illustrates the difficulties one might have in defining the onset of systole in this valvular defect.

The technique appears similar to, if not identical with, that described by Henny and Boone in this country (Electrokymograph for Recording Heart Motion Utilizing the Reontgenoscope. Am. J. Roentgenol. 54:217 (Sept.), 1945).

HECHT.

Marchal, M.: The Registration of Pulsations of the Lung Parenchyma and the Cardiovascular System by Kine-Densigraphy. Arch. d. mal. du coeur 39:345 (Oct.), 1946.

Another method of obtaining electrokymograms is described which appears similar to that reported by Henny and Boone, and by Lian and Minot. Records are obtained from the right and left ventricular borders, pulmonary artery, aorta, and auricles. By placing the photoelectric cell over the pulmonary parenchyma, records may be obtained of the otherwise invisible pulsations of the pulmonary capillaries, veins, and arteries. The method may be of value in detecting stasis or alteration in flow within the pulmonary circulatory system.

HECHT.

Anrep, G. V., Barsoum, G. S., Kenawy, and Misrahy, G.: Ammi Visnaga in the Treatment of the Anginal Syndrome. Brit. Heart J. 8:171 (Oct.), 1946.

The authors report the results of their investigation of the action of khellin on the cardiovascular system with special reference to its effect on the coronary circulation and the heart muscle, and its action in patients suffering from angina pectoris and coronary thrombosis. Experiments were made on dogs, using both the heart-lung preparation and the intact animal.

The minimal active concentration of khellin in the heart-lung preparation is about 1 in 2,000,000. With concentrations of the order of 1 in 2,000,000 the coronary blood flow increases three to four times the initial volume. The action of khellin is less than that of amyl nitrite, but it has the advantage of being much more prolonged. Gradual administration of doses as high as 100 mg. causes no change in the heart volume. Doses many times greater than those causing a conspicuous coronary vasodilatation have no injurious effects on the heart muscle. Electrocardiograms taken before and after administration of khellin were found to be identical in all respects. The pulmonary blood pressure and the rate of the denervated heart were not affected. Intravenous injections of khellin produced a temporary fall in the blood pressure, but this occurred only on rapid administration of large doses. Immediately after a rapid injection of 20 to 30 mg., the blood pressure drops to about 50 mm. Hg, the heart beats considerably slower, and the respiration is momentarily arrested. The effect lasts for only a short time. Slow intravenous injections at the rate of 2 mg. in 20 to 30 seconds can be continued for a long time without ill effects. Doses of 40 to 50 mg. per kilogram cause a prolonged fall of the general blood pressure due to peripheral vasodilatation, mainly of the splanchnic area. Khellin exerts no stimulating effect on the sympathetic nervous system. The apparently selective action of khellin in ordinary dosage on the coronary blood vessels is due to their much greater sensitivity to the drug as compared with the systemic blood vessels.

Khellin was given to forty-six patients, of whom thirty-eight had angina pectoris on effort or at rest and eight had coronary thrombosis. The duration of anginal symptoms was 3 to 12 years in fourteen cases, 1 to 2 years in seventeen, and less than a year in seven. Abnormal electrocardiograms were recorded in seventeen patients, and enlargement of the heart and aorta was found in four patients. As a control, injections free from khellin or containing a much reduced dose were substituted. Doses of 10 to 30 mg. per day by injection were found to be ineffective. A dose of 60 mg. per day gave encouraging results; and 90 to 120 mg. a day yielded better results. Single doses of 150 to 200 mg. were given without ill effect. An average effective dose proved to be 90 mg. a day. The injections caused slight and transient local pain. The average oral dose used was 40 mg. three times daily. The response to khellin was classed as good when the anginal attacks ceased altogether or became very infrequent and mild, as moderate when they diminished in frequency and severity, and negative when no change in the character of the pain occurred. Twenty-eight patients gave a good response, seven patients gave a moderate response, and three gave a negative response.

Khellin was given orally or by injection in doses of 90 to 120 mg. daily for two to five weeks after the onset of coronary thrombosis in eight patients, in six of whom there were recurrent anginal attacks during the period of recumbency. It was well tolerated and, as far as could be judged, relieved the spasmodic anginal attacks that followed the initial attack of pain.

BELLET.

Campbell, M.: Dissecting Aneurysm With Survival for Three Months After Rupture Into the Pleura. Brit. Heart J. 8:200 (Oct.), 1946.

The author reports a case of dissecting aneurysm in which the patient survived for three months after a considerable amount of blood had ruptured into the pleural cavity.

A woman was admitted to the hospital with the history of very severe chest pain followed by collapse. The blood pressure on admission was 120/100 but soon rose to 220/130 and remained at this level after the first two days. She was found to have a left-sided pleural effusion. Aspiration one week later yielded almost pure blood. Her hemoglobin had fallen to 55 per cent and there was a leucocytosis of 15,000 with a normal differential count. The electrocardiogram showed slight inversion of T₁ and there was no significant change in the tracing a week later. At the end of two months she was allowed to be out of bed. After another month she collapsed, became unconscious, and died.

Post-mortem examination revealed that in the arch of the aorta there was a recent tear, with an escape of blood into the lung and pleural cavity. Nine centimeters below the fatal tear, there was an old transverse tear 1.5 cm. long. The dissection extended below this and the stratified clot at this point looked at least as old as, and probably older than, the clot at any other site.

It was not certain if this was the point of re-entry, or if it was the original tear causing the dissection that had spread upward and had ruptured into the lungs and the pleura near the point where the final tear had caused death.

BELLET.

Nissim, J. A.: Dissecting Aneurysm of the Aorta: A New Sign. *Brit. Heart J.* 8:203 (Oct.), 1946.

In a case of proven dissecting aortic aneurysm which began at a point about 4 cm. above the aortic ring, the author encountered a physical sign to which he directs attention. There was a difference in the pulsation of the right and left common carotid arteries. The pulse was reduplicated in the right artery and single in the left artery, without noticeable difference in the strength of the pulsation on the two sides. The author feels that the explanation for this sign must lie in the difference of the rate of propagation of the pulse wave throughout the lumen of the artery, and through its dissected coats where the blood was probably partly clotted. This author suggests that this sign may be observed in other patients and may occur in other arteries.

BELLET.

Ashworth, H., and Jones, A. M.: Aneurysmal Dilation of the Left Auricle With Erosion of the Spine. *Brit. Heart J.* 8:207 (Oct.), 1946.

The authors present a case which is unusual because the enlarged left auricle eroded the vertebral column, produced severe pain in the right chest, and became adherent to the right chest wall, leading to systolic retraction in the right axilla.

A single woman, 38 years of age, was admitted to the Manchester Royal Infirmary because of severe pain in the right chest of four years' duration. Her health had been good until the age of 22, when she developed rheumatic fever. At the age of 36 years she was found to have severe mitral stenosis with gross cardiac enlargement and uncontrolled auricular fibrillation. The left auricle was markedly dilated. At the age of 38 years she was readmitted to the hospital because her pain had become severe and almost continuous. The pulse was completely irregular, rate 136 a minute; the blood pressure, 130/90. Two days after admission normal rhythm with a prolonged P-R interval was recorded. Attacks of regular tachycardia lasting some hours persisted until her death seven weeks later.

Necropsy revealed the finding mentioned. The bodies of the fifth, sixth, seventh, eighth, and ninth thoracic vertebra were eroded; the intervertebral discs were spared.

BELLET.

Christensen, B. C.: Studies on Hyperventilation II. Electrocardiographic Changes in Normal Man During Voluntary Hyperventilation. *J. Clin. Investigation* 25:880 (Nov.), 1946.

Four normal women, 15, 17, 30, and 42 years of age, voluntarily hyperventilated for three to eight minutes. Leads I, II, and III, and in some tests, Lead IVR were recorded during the period of voluntary hyperventilation. Tabulation of data and reproduction of electrocardiograms disclose the following changes during hyperventilation with room air: (1) sinus tachycardia, (2) a slight reduction in conduction time, (3) a reduction in the Q-T interval, (4) depression of the S-T segment 3 or more mm. in two or more leads, and (5) isoelectric, diphasic, or inverted T waves in two or more leads. There were no consistent changes in the heights of the P or R waves. Ten minutes after resumption of normal respiration the electrocardiograms were normal.

Continuation of the hyperventilation in pure oxygen did not abolish the electrocardiographic changes except in one subject. Continuation of the hyperventilation in a gas mixture containing 5 per cent carbon dioxide, 20 per cent oxygen and 75 per cent nitrogen caused the electrocardiograms of all four subjects to return to normal in thirty to sixty seconds.

Two milligrams of nitroglycerin given to two subjects just prior to hyperventilation had no influence upon the occurrence of electrocardiographic changes.

Although reduced carbon dioxide tension shifts the oxygen dissociation curve to the left and makes oxygen less available to the tissues, the author calculates that the deficit can nearly be restored when the hyperventilating subject breaths pure oxygen, by virtue of the increased quantity of oxygen in simple physical solution. Since only one subject's electrocardiographic changes reverted to normal while hyperventilating with pure oxygen, the author implies that the myocardial hypoxia of hyperventilation is not due to an inadequate supply of oxygen. Further, since nitroglycerin does not influence the electrocardiographic changes of hyperventilation, coronary vasoconstriction due to hypocapnia and alkalosis must be unimportant in causing the electrocardiographic changes. The author believes, therefore, that increased intramyocardial tension due to hypocapnia interferes with coronary blood flow.

It is suggested that the electrocardiographic changes in febrile diseases, muscular exercise, effort syndrome, and the hypoxemia test of coronary insufficiency may be influenced by hyperventilation.

FRIEDLAND.

Breda, R., and Costa, F.: Right-Sided Ectatic Aorta. *Folia Card.* 5:461 (Dec. 31), 1946.

A case of right-sided aortic arch with marked dilatation of the first part of the descending aorta is described. The patient was a 55-year-old woman who complained of difficulty in swallowing, which had been present for some time, and palpitation. The signs of Oliver, an inverted sign of Cardarelli, and a severe pulsation in the right supraclavicular and suprasternal areas were present. There was dullness at the right of the sternum. The x-ray showed typical signs of a right-sided aorta, and an esophagus which, because of dilatation of the descending aorta, presented the shape of an inverted S.

LUISADA.

Sossai, A.: On a Case of Spontaneous Rupture of the Heart With Long Survival. *Folia Card.* 5:511 (Dec. 31), 1946.

A case of spontaneous rupture of the heart with survival of nineteen days is described. The patient was a 47-year-old man who suddenly complained of epigastric and retrosternal pain, dyspnea, and vomiting. Fever, fainting episodes, and jaundice followed.

After ten days, the area of precordial dullness became very large and triangular in shape. At the apex, a soft, blowing systolic murmur, becoming harsh at its end, was heard. Leucocytosis, anemia, and an electrocardiogram which was not typical of infarction were found. X-ray showed pericardial effusion, and exploratory paracentesis of the pericardium revealed fluid blood.

Autopsy revealed an acute disseminated myocarditis, fibrinous pericarditis, and hemopericardium. The diagnosis, based upon the necropsy, was acute obscure myocarditis, rupture of the left ventricle, hemopericardium, and pericarditis. The long survival (nineteen days) is undoubtedly a rare occurrence. The type of murmur is analyzed in detail and may have some diagnostic importance.

LUISADA.

Govier, W. M., Yanz, N., and Grelis, M. E.: The Effect of α -Tocopherol Phosphate, Digitoxin, and Certain Compounds Related to the Latter on Cardiac Muscle Metabolism in Vitro. *J. Pharmacol. & Exper. Therap.* 88:373 (Dec.), 1946.

Anoxia of the myocardium may be one of the factors involved in congestive failure. Both α -tocopherol (vitamin E) deficient muscle and cardiac muscle in congestive failure are known to have low creatine levels. This might suggest avitaminosis E in both cases. This, in turn, could lead to coenzyme I breakdown, resulting in damage to cardiac metabolism.

It was found that, in vitro, addition of digitoxin to an anaerobic, E-deficient, lactic dehydrogenase system of guinea pig heart muscle results in a marked stimulation of the system, (increased oxygen uptake and carbon dioxide production). This does not occur in normal heart muscle or in aerobic lactic enzyme systems, normal or α -tocopherol deficient.

This effect is probably due to inhibition of coenzyme I nucleotidase by digitoxin. A-tocopherol also protects coenzyme I breakdown. Ouabain, digitonin, cholesterol, estrone, and testosterone have effects similar to those of digitoxin, to a lesser degree in the case of the hormones.

The work suggests that this action of digitoxin is to preserve cozymase by inhibition of cozymase nucleotidase, thus allowing a more normal metabolism.

GODFREY.

Jokl, E., and Melzer, L.: Rheumatic Fever Following Athletic Trauma. *Acta med. orient.* 6:9 (Jan.) 1947.

These authors report two cases of trauma to large joints which they believed precipitated an attack of acute rheumatic fever with involvement of the heart.

The first case is that of a boy, aged 17 years, who received a kick in the right hip while playing football. A fortnight later he became delirious and developed neck rigidity, with signs of pleurisy and pneumonia. This was followed by acute endocarditis. During the ensuing two days the patient's temperature rose to 106° F., and death occurred soon afterward. Necropsy revealed a hypertrophied left ventricle and a fresh large crumbling thrombotic mass protruding from the ventricular surface of the anterior leaflet of the mitral valve. A small ruptured aneurysm was present beneath the thrombus that was attached to the valve. The cause of death, in the opinion of the authors, was acute rheumatic fever associated with infective endocarditis.

The second case is that of a racing cyclist, aged 21 years, who fell during a training ride and sustained an injury to his left knee. On the following day the affected joint was swollen, and a few days later the other large joints became swollen accompanied by a temperature of 104° Fahrenheit. Subsequently, the patient was admitted to a hospital where a diagnosis of rheumatic fever and cardiac involvement was made. Within the following three weeks the swelling of his joints subsided, his temperature returned to normal, but his heart "remained bad." Roentgen examination revealed an enlarged heart and the electrocardiogram suggested right preponderance. After the preceding episode, the patient experienced pain in the cardiac region and dyspnea on slight exertion, and he was no longer able to continue his athletic career. There was no improvement in this patient's condition during a five-year period of observation.

BELLET.

Dreyfuss, F.: An Observation Concerning the Hands of Patients With Rheumatic Fever. *Acta med. orient.* 6:12 (Jan.), 1947.

The author draws attention to the fact that individuals who present rheumatic valvular lesions, a history of rheumatic fever, or are ill with acute rheumatic fever frequently have a particular shape of hand. Their palms usually show a tendency to be long and slender, their fingers are usually rather long, somewhat pointed, and tapering. These fingers usually do not show any prominence at the level of their interphalangeal joints. The nearer the diameter of the finger is taken to its root, the larger it is. These fingers are usually straight. Corresponding to the general appearance of many of these patients, their hands are also usually pale and often remarkably flexible. Their skin is occasionally somewhat dark above the interphalangeal joints.

The author observed this type of hand in the majority of patients with rheumatic fever or rheumatic heart lesions, more frequently in females than in males. In a series of forty-five patients (ten males, and thirty-five females) who had either active rheumatic fever with and without carditis or inactive rheumatic heart disease, this type of hand was observed in thirty-seven cases (eight males and twenty-nine females, respectively). Noting such a hand in a male patient is more striking than in a female. It serves as a hint, particularly in routine examination on patients, and should lead one to look for evidence of rheumatic involvement.

The shape of fingers described also is noted frequently in normal individuals who have no history of rheumatic fever and present no rheumatic lesions. Often relatives of rheumatic fever patients possess this type of hand.

The author believes that the occurrence of this type of hand in healthy people and particularly in relatives of patients with rheumatic fever leads one to assume that these hands are a manifestation of a constitutional type disposed to rheumatic fever, and not a result of disease.

BELLET.

Davis, L., and Perret, G.: Cerebral Thromboangiitis Obliterans. *Brit. J. Surg.* 34:307 (Jan.), 1947.

The authors emphasized the point brought out by a number of workers that thromboangiitis obliterans is a generalized pathologic process affecting vessels not only in the extremities but also in many other sites of the body. The paper deals with the findings observed in eleven cases in which the cerebral vessels were involved. In only three of these was there any evidence of peripheral circulatory disturbances.

The authors state that the condition is not as rare as might be expected, but that the purely cerebral form presents many diagnostic difficulties. In fact, it has been mistaken for other pathologic entities such as syphilis, juvenile arteriosclerosis, hypertension, and intracranial tumors.

In nine of the eleven reported cases an osteoplastic craniotomy was performed, and in each instance the dura mater was loose and boggy, the arachnoid was thickened and opaque, and the subarachnoid space was distended with cerebrospinal fluid. The predominating pathologic change was segmental obliteration of the distal portions of the smaller cerebral arteries and, to a lesser extent, of the smaller cerebral veins. There was an associated yellowish discoloration, softening, and atrophy of disseminated cortical areas in the field of the occluded vessels.

The findings in the involved arteries consisted of proliferation of the intimal and subintimal cells, with little or no change in the media and adventitia. Large thrombi in various stages of organization completely obliterated the lumen of the vessels. Fresh inflammatory reactions were noted in the intima of obliterated vessels in the cases which subsequently came to autopsy.

The clinical diagnosis of cerebral thromboangiitis obliterans is based on a history of long duration of transient but progressive cerebral symptoms, evidence of cerebral atrophy in pneumoencephalograms, and possible peripheral vascular changes in the eye grounds and in the extremities. Obviously, when the condition is limited to the cerebral vessels, the diagnosis is difficult to make.

ABRAMSON.

Raab, W., and Humphreys, R. J.: Drug Action Upon Myocardial Epinephrine-Sympathin Concentration and Heart Rate (Nitroglycerine, Papaverine, Priscol, Dibenamine Hydrochloride). *J. Pharmacol. & Exper. Therap.* 88:64 (Jan.), 1947.

The paper deals with artificial cardiac acceleration in the cat by means of intravenous epinephrine (atropinized specimen), stimulation of the stellate and splanchnic ganglia, and intravenous acetylcholine (atropinized specimen). In the controls, cardiac acceleration and the accumulation of epinephrine-sympathin-like substances in the myocardium were measured. The same type of experimental preparations, stimulated in the same manner, were given nitroglycerine, papaverine, priscol, and dibenamine hydrochloride.

In the controls, epinephrine produced a marked rise in pulse rate, and a massive increase of 990 per cent in the amount of epinephrine-like substance in the myocardium. Stellate and splanchnic ganglia stimulation and acetylcholine injection produced a marked rise in pulse rate, but only 21 to 35 per cent increase in epinephrine-like substance in the myocardium. Nitroglycerine markedly decreased the acceleration, but only moderately affected the accumulation of epinephrine-like substance (990 per cent to 914 per cent in animals injected with epinephrine). Papaverine practically abolished cardiac acceleration and markedly diminished accumulation of epinephrine-like substance (990 per cent to 566 per cent). Priscol and dibenamine hydrochloride both showed marked slowing effects. Dibenamine hydrochloride reduced the concentration of epinephrine-like substance from 35 per cent to 7 per cent in the stellate ganglion preparations. Priscol did not greatly influence the accumulation.

The fact that all preparations had a marked effect on acceleration, but differed greatly in inhibiting the accumulation of epinephrine-like substance, suggests that the antagonistic action against adrenosympathetic cardiac stimulation differs from drug to drug.

If epinephrine accumulates in the myocardium in angina pectoris, this work suggests that the action of nitroglycerine and papaverine may be twofold: desensitization of the myocardium to epinephrine, and coronary dilatation.

GODFREY.

Castro, V. A., and Rubio, Carlos W.: Significado de Algunas Alteraciones de las Ondas T. Arch. Inst. cardiol. Mexico 16:98 (Feb.), 1947.

The appearance of the electrocardiogram can be modified by means of carotid sinus pressure; typical T waves (notched, flat, isoelectric, diphasic) tend to become inverted, and negative T waves tend to become more deeply inverted. These changes are transitory, but when pressure is combined with massage of the carotid sinus they may last a long time, because bradycardia and hypotension may continue for thirty minutes or more.

The effect of carotid sinus pressure is opposite to that of effort. The combination of both procedures can quickly and considerably change the shape of the T waves, without appreciably modifying the QRS complex.

AUTHORS.

Rosenblueth, A., and Ramos, J. Garcia: Action of Artificial Obstacles on Experimental Flutter. Arch. Inst. cardiol. Mexico 17:1 (Feb.), 1947.

The authors studied the conditions which favor the appearance of auricular flutter in the dog after cutting both vagi and sympathetics. The easiest way to obtain such a rhythm is to block the conduction of impulses between the openings of the two venae cavae. This can be done either by the use of cocaine or by crushing the myocardium; the following auricular flutter continues as long as the block is present.

This abnormal rhythm is not initiated in the sinoauricular node. Its rate is accelerated by stimulation of the vagus or injection of adrenaline. Additional injuries in the damaged area decrease the rate of the flutter. Flutter can be obtained only if the damaged area is surrounded by normal conducting tissue.

LUISADA.

Mendez, R.: General Concept of Digitalis Action. Arch. Inst. cardiol. Mexico 16:83 (Feb.), 1947.

The author discusses the actions of Angelicalactone, a synthetic lactone similar to the lactonic group of digitoxin. The substance exerts a digitalis-like action on the isolated frog heart. The toxicity on cats also might indicate a similarity in its action to digitalis. However, the latter test is inadequate because it merely reveals the toxic, and not the therapeutic activity of a substance. Therefore, the drug was tested on a heart-lung preparation after heart failure had been induced by the use of nembutal. While cardiac glycosides relieve such failure, Angelicalactone fails to do so.

The author concludes that the tested substance has no useful cardiac activity, and suggests a wider use of the heart-lung preparation as a test medium for these drugs.

LUISADA.

Dry, T. J., Edwards, J. E., Maynard, A. E., Moe, A. E., and Vigran, I. M.: Mycotic Aneurysm of the Posterior Tibial Artery Complicating Subacute Bacterial Endocarditis: Antemortem Diagnosis Confirmed by Instrumental Means. Proc. Staff Meet., Mayo Clin. 22:105 (March 19), 1947.

The authors present a case of a 40-year-old man who, a few days prior to admission to the Clinic, experienced pain in the upper part of the left calf. On admission his temperature was 102° F., and classical signs of aortic insufficiency were present. The upper portion of the left

calf was tender and swollen, with small petechiae in the surrounding area. The dorsalis pedis and posterior tibial arteries gave strong pulsations and pistol-shot sounds could be heard clearly along the entire course of all these vessels. The diagnosis of subacute bacterial endocarditis was made and the subcutaneous administration of penicillin in doses of 40,000 units every three hours was begun. This dose was doubled the next day. After the second day of therapy the pain and swelling in the left calf appeared to subside, but on the eighth hospital day the patient again experienced sudden severe pain in this region, the pain extending into the left leg and toes. The pulse in the posterior tibial artery of the left leg was completely absent. The clinical impression was that an infected embolus had lodged in one of the branches of the left posterior tibial artery, and that perforation of the vessel had occurred when the second episode of pain developed.

On the twelfth day the patient had a sudden onset of tachycardia and tachypnea, and coarse moist râles were heard over the bases of the lungs. He died suddenly on the next day.

On post-mortem examination, the heart was found to be enlarged and the leaflets of the aortic valve were ulcerated. The aortic valve showed, in addition, evidence of an ancient inflammatory process (probably rheumatic) in the form of an organized adhesion between the left and right cusps. The left posterior tibial artery contained a thrombus originating at a point 3.7 cm. below the origin of the vessel, and extending downward for a distance of 3 centimeters. At the lower level of the thrombus, the lumen of the vessel was completely occluded and the anterior wall of the vessel was slightly dilated and perforated. Through the perforation the artery communicated with a cavity measuring 3.5 cm. vertically and 2.5 cm. across.

The diagnosis of mycotic aneurysm was suspected clinically on the basis of the history, physical signs, and sound recordings of the pulse.

BELLET.

Smith, B. C., and Quimby, E. H.: The Use of Radioactive Sodium in the Study of Peripheral Vascular Disease. Ann. Surg. 125:360 (March), 1947.

Radioactive sodium was utilized to study the circulation time in twenty-five young normal individuals and in patients with arteriosclerosis obliterans, thromboangiitis obliterans, hypertension, frostbite, and immersion foot. The material was prepared in a cyclotron by bombarding sodium metaborate with deuterons. After it was prepared for parenteral administration, it was injected into an antecubital vein and the time of arrival of the radioactive material in the foot was determined by the use of a Geiger counter.

According to the authors, the arrival of the material at an extremity and the nature of its build-up there to equilibrium between intra- and extravascular fluid give useful information regarding the arterial circulation to the limb and, in patients requiring amputation, the site at which healing can be expected.

ABRAMSON.

Priest, Walter S., Smith, Jacques M., and McGee, Charles J.: Penicillin Therapy of Subacute Bacterial Endocarditis. Arch. Int. Med. 79:3 (March), 1947.

The authors analyze the end results of thirty-four consecutive unselected case of penicillin treatment of subacute bacterial endocarditis. After a period of one to three years after institution of treatment, twenty-two of the thirty-five are still not only alive and symptomless but have negative blood cultures.

Streptococcus viridans was the predominant offender, but hemolytic streptococcus, non-hemolytic streptococcus, *Staphylococcus aureus*, *Staphylococcus albus*, *Streptobacillus moniliformis* and *Hemophilus para-influenzae* were also found. In twenty-seven cases a test was made for in vitro sensitivity and found to range from 0.02 to 6.0 units per cubic centimeter.

The most important single factor in the treatment was adequate dosage of penicillin, given over a period of at least four weeks. At least 500,000 units per day should be administered, preferably by intravenous drip with isotonic saline. If intravenous drip seems impractical, the authors recommend 100,000 units intramuscularly every ninety minutes. Factors which would point to the need for higher dosage (1-2 million units daily) are (1) duration of the disease for

twelve weeks or longer, (2) sensitivity in vitro of 0.1 units per c.c. or greater, and (3) lack of response to 500,000 units. It was pointed out that failure occurred in seven of ten cases when a dosage of 400,000 units per day was given.

The authors also felt that (1) limiting fluids to 800 to 900 c.c. during the waking period results in a more constant penicillin level, (2) it was preferable to increase the penicillin dosage rather than to give substances such as para-aminohippuric acid to retard the rate of renal excretion, (3) that anticoagulants were contraindicated, and (4) that the leucocyte count and sedimentation rates were just as valuable, or more so, than the blood culture in determining the activity of the disease.

HORWITZ.

Robertson, Theodore: Paracolon Bacillus Endocarditis of the Pulmonic Valve Secondary to Infected Polycystic Kidneys. Arch. Path. 43:318 (March), 1947.

After a left nephrocystotomy in a 40-year-old white man with polycystic kidneys, a bacteremia developed which did not respond to penicillin, sulfadiazine, or blood transfusions. The patient died with uremia.

Autopsy showed two huge kidneys containing numerous cysts, mostly filled with thick foul-smelling pus. The heart weighed 400 grams and the left ventricle was hypertrophied. The pulmonic valve leaflets were almost destroyed and replaced by large vegetations composed of firm yellow granulation tissue. Many smaller vegetations were ulcerated. The other valves were normal.

The spleen weighed 550 grams, was dark red and firm. Post-mortem cultures of the heart blood, the lung, and of pus from the renal cysts were all positive for the paracolon bacillus. A crushed piece of the pulmonary valve vegetation gave a positive culture for the same organism.

It appeared that there was no chronic valvular damage preceding this vegetative endocarditis. This is the first recorded instance of paracolon endocarditis.

GOULEY.

Jones, A. B.: Peripheral Venous Thrombosis: Preventive Measures and Treatment. M. J. Australia 1:297 (March), 1947.

The author reviewed the literature regarding the incidence of peripheral venous thrombosis and the generally accepted procedures utilized in the prevention of this condition, as well as the medical and surgical treatment. No new concepts were discussed nor was any attempt made to elaborate upon any controversial points.

ABRAMSON.

Olson, W. H., and Necholes, H.: Studies on Anuria: Effect of Infusion Fluids and Diuretics on the Anuria Resulting From Severe Burns. Surg., Gynec. & Obst., 84:283 (March), 1947.

The authors, by means of severe burns in anesthetized dogs in acute experiments, have correlated the urinary output with the hematocrit and the degree of hemoglobinemia. They observed, along with others, that the anuria associated with severe burns, the crush syndrome, and incompatible blood transfusions are largely due to circulating free hemoglobin and myoglobin and their deleterious effects on the kidney.

In the present paper the authors focus their attention on the study of a variety of diuretics which may have clinical value in the overcoming of the anuria associated with severe burns. They found, confirming Maitland's observation in 1941, that infusions of isotonic sodium sulfate were vastly superior to any other diuretic studied and that it was the only one which would effect a good diuresis in the presence of high blood levels of hemoglobin. Plasma and saline were the least effective solutions.

LORD.

Robles Gil, J.: Clinical and Histopathological Study of the Nodules in Various Rheumatic Diseases. Arch. Inst. cardiol. México 17:169 (April 30), 1947.

The nodules of various rheumatic diseases were studied from a clinical and histologic point of view. A comparison of the findings with similar findings reported from other countries was also made. Biopsy was done in many subjects.

The cases include 205 patients with rheumatoid arthritis, 667 with rheumatic fever, 183 with osteoarthritis, and 35 with gout. No difference was found between these nodules and those described in other countries. The clinical and histological aspects of the nodules in rheumatic fever and rheumatoid arthritis seem to show: (a) that they are different diseases; (b) that they are real pathologic entities and not syndromes caused by various agents; (c) that the nodules are similar to those observed in certain chronic infectious diseases, though different in some aspects; (d) that they are similar to lesions found in other organs of the same patients; and (e) that they are signs of activity of the process and have a definite prognostic importance.

Heberden nodes are the result of a degenerative process, similar to that observed in several joints of the same patients. Chronic trauma and circulatory and endocrine disturbances seem to play a certain role in the osteoarthritic manifestations.

Differential diagnosis is considerably helped by biopsy with histologic study of the nodules.

LUISADA.

Ortiz Ramirez, T.: Variations of Cardiac Pain Caused by Respiration, Postural Changes, and Pressure. Arch. Inst. cardiol. México 17:224 (April 30), 1947.

Cardiac pain may be accompanied by manifestations which are commonly thought to be typical of pain due to other causes. Breathing, changes in the position of the body, and external pressure may increase cardiac pain. The author explains this fact by the theory of "referred pain." He further points out that some of the accepted methods for differentiating "cardiac pain" from "thoracic pain" have no actual value.

LUISADA.

Salazar Mellen, M., Lozano Lube, E., and Brenes, M.: A Comparative Study of Cultures of Arterial or Venous Blood and Bone Marrow in Patients With Subacute Bacterial Endocarditis. Arch. Inst. cardiol. México 17:229 (April 30), 1947.

The authors studied 327 samples of bone marrow and arterial and venous blood from eighty-eight clinical cases, diagnosed as having subacute bacterial endocarditis. All three types of cultures were positive in twelve cases. Bone marrow cultures were positive in twenty-one cases, arterial blood cultures in fifteen, and venous blood cultures in nineteen.

The cultures made with arterial blood were never positive when the others were negative. Cultures of bone marrow were positive when blood cultures were negative, but only in patients under penicillin treatment.

In conclusion, cultures of bone marrow may be helpful where technical difficulties for arterial or venous cultures are present or in doubtful cases. Moreover, they may permit us to ascertain when a case of subacute bacterial endocarditis is cured.

LUISADA.

Krontiris, A.: Experiences With Sympathectomy for Sequelae of Trench Feet. Ann. Surg. 125:505 (April), 1947.

Twenty-seven patients demonstrating the late sequelae of trench foot were subjected to lumbar sympathetic ganglionectomy. The immediate results consisted of alleviation of pain in the affected foot and disappearance of hyperhidrosis. The delayed results were studied with regard to ulcerations. Those lesions situated in the lower part of the leg healed rapidly and permanently, while little effect was noted in those instances in which the foot, particularly the heel, was involved. In the case of the latter, plastic repair was subsequently necessary, and this procedure in most instances was successful. However, the author was inclined to believe that the prolonged period of rest in bed, rather than the sympathectomy, was responsible for the

therapeutic results. The author concluded that sympathectomy in the treatment of the sequelae of trench feet produced a temporary reduction in pain and in the vasomotor instability, while it had a doubtful and uncertain therapeutic effect on the healing of ulcerations.

ABRAMSON.

Hufnagel, C. A.: Permanent Intubation of the Thoracic Aorta. Arch. Surg. 54:383 (April), 1947.

The author reviews the methods of the nonsuture technique of vascular anastomosis and points out defects and limitations of each of them. For the first time, by means of highly polished lucite (methyl methacrylate) tubes, Hufnagel was able to intubate the thoracic aorta of dogs and have the tubes remain patent indefinitely. The plastic, lucite, possesses the quality of delaying coagulation of the blood due to its pronounced water-repellent surface. One important problem was overcome when the author found that multiple braids of braided silk (U. S. P. No. 2) did not crush the wall of the aorta and held the tube satisfactorily. No clinical material was presented.

LORD.

Mylks, G. W., Brown, A. B., and Robinson, C. N.: Air Embolism During Labour. Canad. M. A. J. 35:427 (April), 1947.

The purpose of this report is to record a case of air embolism as a complication of labor.

A white woman, 32 years of age, showed considerable edema of the feet, ankles, and legs in approximately her eighth month of pregnancy. Her weight had risen over 18 pounds in six weeks, the blood pressure was 162/94, and urine contained a heavy trace of albumin. She was admitted to the hospital and put on a high protein, low salt diet. During the ten days spent in the hospital her blood pressure fell to 122/82 and she lost 14 pounds in weight. Induction of labor was attempted, but failed. Soon thereafter labor began spontaneously.

At the onset of labor she experienced a chill, her temperature rose to 101° F., vomiting occurred, she became very restless and was cyanosed, and went into shock. The pulse at this time was 150 per minute and the systolic blood pressure was below 80 mm. Hg. She was given a blood transfusion in one arm and distilled water with 10 per cent glucose in the other. The fetal heart rate was 120 beats per minute. Oxygen inhalation was administered. The baby was stillborn and the patient died.

Autopsy, performed two hours after death, showed the first evidence of the cause of death when the vessels of the breast were cut and air bubbles could be seen escaping with the blood. When the heart was compressed and the right ventricle opened, air bubbles rushed out. On opening the chest both lungs were found collapsed.

In this case of air embolism during labor no other mode of entry for the air seems plausible except through the uterine sinuses. The authors explain that the air reached the systemic circulation because the air bubbles became so reduced in size from absorption that they were able to pass to the left side of the heart. It is noted that most reported cases of air embolism associated with labor have usually been preceded by operative interference.

BELLET.

Lupton, A. M.: The Effect of Perfusion Through the Isolated Liver on the Prothrombin Activity of Blood From Normal and Dicumarol Treated Rats. J. Pharmacol. & Exper. Therap. 89:306 (April), 1947.

Liver from both normal rats and rats that had been given dicumarol prior to sacrifice were isolated and perfused through the portal vein. Blood was drawn from both normal and dicumarol-treated rats. The blood was citrated, perfused continuously for two hours, and tested frequently for prothrombin activity.

Normal blood perfused through the liver of normal rats showed no change in prothrombin activity. Normal blood perfused through livers of dicumarol-treated rats resulted in no change

in the prothrombin activity of the blood. Blood from dicumarol-treated rats perfused through normal livers showed a significant increase in prothrombin activity.

These results suggest that the liver is the site of prothrombin formation.

GODFREY.

Kipple, H. M., Waldman, M. S., Hall, V. E.: Cardiovascular Effects of Sodium Caprylate in the Cat. *J. Pharmacol. & Exper. Therap.* 89:313 (April), 1947.

Using intact cats in the recording of venous and arterial pressure, and ventricular volume in systole and diastole (cardiometer), the results of intravenous injection of Ringer's solution were compared with those following the injection of sodium caprylate in concentrations ranging from 0.075 to 0.75 mm. per kilogram. The results of caprylate injection differed quantitatively from those of Ringer's solution. There was a temporary dilatation of the heart, an increased stroke volume, and an increased cardiac output and venous pressure. With a constant diastolic volume there is a slight increase in stroke volume with sodium caprylate as compared to Ringer's solution. The blood pressure was higher with the former than with the latter. The preceding actions suggest that sodium caprylate has some digitalis-like action on the cat heart.

GODFREY.

Dawes, G. S. L.: Studies on Veratrum Alkaloids. VII. Receptor Areas in the Coronary Arteries and Elsewhere as Revealed by the Use of Veratridine. *J. Pharmacol. & Exper. Therap.* 89:325 (April), 1947.

Veratrum alkaloids are known to cause a fall in blood pressure and heart rate. Impulses for this action are believed to arise from the afferent cardiac branches of the vagi; the effect on the heart is abolished by section of the vagi.

The coronary arteries and their branches in intact cats and dogs were canalized and their circulation kept intact by means of arterial anastomosis, leaving them available for direct intra-arterial injection. Injection of veratridine into the femoral artery results in a smaller fall in blood pressure and pulse rate than when the same concentration is injected into the left ventricle. Minute amounts of drug (0.1 to 0.25 microgram) injected into the coronary arteries produces a marked fall in blood pressure and pulse rate.

Injection into branches of the coronary arteries supplying the left ventricle had a maximum effect.

Veratridine injected into the perfused left lung also causes a fall of blood pressure and heart rate; however, larger doses must be used than in the coronary circulation.

Veratridine potentiates the action of potassium chloride on the central nervous system in causing a fall in blood pressure and heart rate and reduction in depth and rate of respiration.

GODFREY.

Copley, A. L., and Stefkó, P. L.: Coagulation Thrombi in Segments of Artery and Vein in Dogs and the Genesis of Thromboembolism. *Surg., Gynec. & Obst.* 84:451 (April), 1947.

The purpose of the experimental study was to determine whether tissue juice from veins of homologous and heterologous origin would coagulate the stagnant blood within a formed vessel segment in vivo. The investigation was performed on dogs, using the carotid and femoral arteries and the jugular and femoral veins.

Tissue juice from veins of dogs and chickens induced coagulation thrombi in segments of arteries, while tissue juice from veins of dogs produced this response in segments of veins. Human placental thromboplastin induced coagulation thrombi in both arteries and veins. The authors found that in the absence of infection the coagulation thrombi were nonadherent to the vessel wall and exhibited clot retraction. Attention was called to the similarity of this type of thrombus to the entity of phlebothrombosis with regard to embolus formation. Physiologic saline, used as a control, did not cause coagulation thrombi nor did mechanical manipulations. Crushing of the vessel segment over silk produced the response on occasion.

therapeutic results. The author concluded that sympathectomy in the treatment of the sequelae of trench feet produced a temporary reduction in pain and in the vasomotor instability, while it had a doubtful and uncertain therapeutic effect on the healing of ulcerations.

ABRAMSON.

Hufnagel, C. A.: Permanent Intubation of the Thoracic Aorta. Arch. Surg. 54:383 (April), 1947.

The author reviews the methods of the nonsuture technique of vascular anastomosis and points out defects and limitations of each of them. For the first time, by means of highly polished lucite (methyl methacrylate) tubes, Hufnagel was able to intubate the thoracic aorta of dogs and have the tubes remain patent indefinitely. The plastic, lucite, possesses the quality of delaying coagulation of the blood due to its pronounced water-repellent surface. One important problem was overcome when the author found that multiple braids of braided silk (U. S. P. No. 2) did not crush the wall of the aorta and held the tube satisfactorily. No clinical material was presented.

LORD.

Mylks, G. W., Brown, A. B., and Robinson, C. N.: Air Embolism During Labour. Canad. M. A. J. 35:427 (April), 1947.

The purpose of this report is to record a case of air embolism as a complication of labor. A white woman, 32 years of age, showed considerable edema of the feet, ankles, and legs in approximately her eighth month of pregnancy. Her weight had risen over 18 pounds in six weeks, the blood pressure was 162/94, and urine contained a heavy trace of albumin. She was admitted to the hospital and put on a high protein, low salt diet. During the ten days spent in the hospital her blood pressure fell to 122/82 and she lost 14 pounds in weight. Induction of labor was attempted, but failed. Soon thereafter labor began spontaneously.

At the onset of labor she experienced a chill, her temperature rose to 101° F., vomiting occurred, she became very restless and was cyanosed, and went into shock. The pulse at this time was 150 per minute and the systolic blood pressure was below 80 mm. Hg. She was given a blood transfusion in one arm and distilled water with 10 per cent glucose in the other. The fetal heart rate was 120 beats per minute. Oxygen inhalation was administered. The baby was stillborn and the patient died.

Autopsy, performed two hours after death, showed the first evidence of the cause of death when the vessels of the breast were cut and air bubbles could be seen escaping with the blood. When the heart was compressed and the right ventricle opened, air bubbles rushed out. On opening the chest both lungs were found collapsed.

In this case of air embolism during labor no other mode of entry for the air seems plausible except through the uterine sinuses. The authors explain that the air reached the systemic circulation because the air bubbles became so reduced in size from absorption that they were able to pass to the left side of the heart. It is noted that most reported cases of air embolism associated with labor have usually been preceded by operative interference.

BELLET.

Lupton, A. M.: The Effect of Perfusion Through the Isolated Liver on the Prothrombin Activity of Blood From Normal and Dicumarol Treated Rats. J. Pharmacol. & Exper. Therap. 89:306 (April), 1947.

Liver from both normal rats and rats that had been given dicumarol prior to sacrifice were isolated and perfused through the portal vein. Blood was drawn from both normal and dicumarol-treated rats. The blood was citrated, perfused continuously for two hours, and tested frequently for prothrombin activity.

Normal blood perfused through the liver of normal rats showed no change in prothrombin activity. Normal blood perfused through livers of dicumarol-treated rats resulted in no change

in the prothrombin activity of the blood. Blood from dicumarol-treated rats perfused through normal livers showed a significant increase in prothrombin activity.

These results suggest that the liver is the site of prothrombin formation.

GODFREY.

Kipple, H. M., Waldman, M. S., Hall, V. E.: Cardiovascular Effects of Sodium Caprylate in the Cat. *J. Pharmacol. & Exper. Therap.* 89:313 (April), 1947.

Using intact cats in the recording of venous and arterial pressure, and ventricular volume in systole and diastole (cardiometer), the results of intravenous injection of Ringer's solution were compared with those following the injection of sodium caprylate in concentrations ranging from 0.075 to 0.75 mm. per kilogram. The results of caprylate injection differed quantitatively from those of Ringer's solution. There was a temporary dilatation of the heart, an increased stroke volume, and an increased cardiac output and venous pressure. With a constant diastolic volume there is a slight increase in stroke volume with sodium caprylate as compared to Ringer's solution. The blood pressure was higher with the former than with the latter. The preceding actions suggest that sodium caprylate has some digitalis-like action on the cat heart.

GODFREY.

Dawes, G. S. L.: Studies on Veratrum Alkaloids. VII. Receptor Areas in the Coronary Arteries and Elsewhere as Revealed by the Use of Veratridine. *J. Pharmacol. & Exper. Therap.* 89:325 (April), 1947.

Veratrum alkaloids are known to cause a fall in blood pressure and heart rate. Impulses for this action are believed to arise from the afferent cardiac branches of the vagi; the effect on the heart is abolished by section of the vagi.

The coronary arteries and their branches in intact cats and dogs were canalized and their circulation kept intact by means of arterial anastomosis, leaving them available for direct intra-arterial injection. Injection of veratridine into the femoral artery results in a smaller fall in blood pressure and pulse rate than when the same concentration is injected into the left ventricle. Minute amounts of drug (0.1 to 0.25 microgram) injected into the coronary arteries produces a marked fall in blood pressure and pulse rate.

Injection into branches of the coronary arteries supplying the left ventricle had a maximum effect.

Veratridine injected into the perfused left lung also causes a fall of blood pressure and heart rate; however, larger doses must be used than in the coronary circulation.

Veratridine potentiates the action of potassium chloride on the central nervous system in causing a fall in blood pressure and heart rate and reduction in depth and rate of respiration.

GODFREY.

Copley, A. L., and Steffko, P. L.: Coagulation Thrombi in Segments of Artery and Vein in Dogs and the Genesis of Thromboembolism. *Surg., Gynec. & Obst.* 84:451 (April), 1947.

The purpose of the experimental study was to determine whether tissue juice from veins of homologous and heterologous origin would coagulate the stagnant blood within a formed vessel segment in vivo. The investigation was performed on dogs, using the carotid and femoral arteries and the jugular and femoral veins.

Tissue juice from veins of dogs and chickens induced coagulation thrombi in segments of arteries, while tissue juice from veins of dogs produced this response in segments of veins. Human placental thromboplastin induced coagulation thrombi in both arteries and veins. The authors found that in the absence of infection the coagulation thrombi were nonadherent to the vessel wall and exhibited clot retraction. Attention was called to the similarity of this type of thrombus to the entity of phlebothrombosis with regard to embolus formation. Physiologic saline, used as a control, did not cause coagulation thrombi nor did mechanical manipulations. Crushing of the vessel segment over silk produced the response on occasion.

The authors devoted a considerable portion of their paper to a review of the literature and a discussion of the various factors responsible for intravascular blood clotting and for the formation of thromboembolism.

ABRAMSON.

Thebaut, B. R., and Ward, C. S.: Ligation of the Inferior Vena Cava in Thrombo-Embolism. Surg., Gynec. & Obst. 84:385 (April), 1947.

The paper deals with the controversial subject of the treatment of pulmonary embolism. The authors advocate venous ligation at high levels and, in support of their view, present the results obtained with ligation of the inferior vena cava in thirty-six patients suffering from pulmonary embolism having its origin in the deep veins of the lower extremities. It is the author's belief that this procedure should be used routinely under such circumstances, since it offers the patient the best prognosis for both immediate and ultimate results. They are not impressed by the therapeutic use of anticoagulants in preventing further episodes of pulmonary embolism in a patient already suffering from this condition, although they acknowledge the value of the treatment as a prophylactic measure before thrombosis has occurred or following ligation of the inferior vena cava, to prevent the thrombotic process from extending into unaffected vessels. They also express disappointment in the treatment of deep thrombosis by proximal venous ligation at levels below the common iliacs, calling attention to the fact that from personal observation and on the basis of reported cases, emboli may recur despite bilateral femoral vein ligation. Even if this procedure is combined with phlebotomy and aspiration of the thrombus, as suggested by some workers, there is still great danger in leaving even a small portion of thrombus or an area of roughened intima in the vein proximal to the site of its interruption, since such a nidus may become the source of a new propagating thrombus and pulmonary emboli.

The authors point out the technical advantage of inferior vena cava ligation, which requires only a single operation, as compared with bilateral femoral vein ligation. At the same time the procedure offers protection not only from emboli arising in the veins at both lower extremities but from a pelvic source as well. The only major disadvantage is that a spinal or general anesthetic is necessary for inferior vena caval ligation, whereas femoral vein ligation can be carried out under local anesthesia. Attention is also directed to the findings reported by several investigators that the collateral circulation following interruption of the common femoral or the external iliac vein is far less satisfactory than that following ligation of the common iliac or the inferior vena cava. Hence, it would be expected that the edema of the extremity would be less severe and of shorter duration following high ligation. This view has been borne out clinically. However, the majority of the patients in the series did have a mild degree of dependent edema in the lower extremities for several months after operation, although in none was this incapacitating. Immediately after the procedure was carried out, in more than half the cases there was a definite aggravation of symptoms in the involved extremity, particularly an increase in edema.

Four of the patients in the series died, two on the operating table, before the vena cava was ligated. One died twenty minutes after closure of the incision, and another five hours later. Two patients in the series developed increased chest pain following operation but recovered completely. X-ray studies confirmed the impression that no new areas of pulmonary infarction had occurred in these individuals.

The technique for ligation of the inferior vena cava and the postoperative care are presented in detail.

ABRAMSON.

Collins, V. J., Foster, W. L., and West, W. J.: Vasomotor Disturbances in Poliomyelitis. With Special Reference to Treatment With Paravertebral Sympathetic Block. New England J. Med. 236:694 (May 8), 1947.

In a group of 131 patients convalescent from poliomyelitis, the authors noted the frequent occurrence of edema, hyperhidrosis, coldness, chilblains, and other manifestations of vasomotor disturbances. The severity of these manifestations did not parallel the extent of the motor paralysis. Lumbar paravertebral sympathetic block was performed on patients with lower extremity

involvement, and stellate ganglion block on those with upper extremity involvement. The technique is described.

All patients treated showed temporary improvement, subjectively and objectively. The duration of improvement increased after each subsequent block. In several cases, after the third or fourth block, the improvement was of many weeks' duration. The efficacy of this treatment in the relief of muscle spasm, tenderness, and pain was of especial interest.

KAY.

Allen, E. V.: The Clinical Use of Anticoagulants. J. A. M. A. 134:323 (May 24), 1947.

The author discussed in detail the action of heparin and dicumarol and their clinical use in intravascular clotting. The exact dosage of the drugs and the treatment of overdosage were also presented.

On the basis of a study of a large series of cases, the author was of the opinion that dicumarol is effective in preventing venous thrombosis or in checking its extension once it has occurred. He concluded that the judicious and expert use of anticoagulants is at least as effective in counteracting pulmonary embolism as is ligation of large veins. However, he did acknowledge that in cases in which there is repeated venous thrombosis and pulmonary embolism, ligation of a vein may be superior to anticoagulant therapy because of the difficulty of administering the latter over a long period. According to the author, the danger of bleeding from the use of anticoagulants is minimal, provided their administration is properly controlled by repeated laboratory tests.

ABRAMSON.

Birchall, R., Taylor, R. D., Lowenstein, V. E., and Page, I. H.: Clinical Studies of the Pharmacologic Effects of Tetraethyl Ammonium Chloride in Hypertensive Persons Made in an Attempt to Select Patients Suitable for Lumbodorsal Sympathectomy and Ganglionectomy. Am. J. M. Sc. 213:572 (May), 1947.

It was reasoned by the authors that, if tetraethyl ammonium chloride had a highly selective depressing action on sympathetic ganglia, it should be possible to estimate pharmacologically the effect on blood pressure of lumbodorsal sympathectomy and ganglionectomy; this would provide a method for selecting candidates suitable for operation. However, the results presented indicate that, in addition to its effect on the sympathetic ganglia, it affects the parasympathetic ganglia and sensory nerve fibers and impairs motor function. Mydriasis and dry mouth represent inhibition of the parasympathetic components. All of the patients studied experienced some degree of numbness and tingling immediately following injection of the drug, which suggested that it acts upon sensory nerve fibers. Its curare-like action was indicated by dysarthria, dysphagia, ptosis, and, finally, intercostal and diaphragmatic paresis.

A drug which acts so diffusely in human beings might be expected to affect the blood pressure in a manner different from that of sympathectomy and ganglionectomy. That this is true is indicated by the fact that the degree of arterial pressure reduction induced in the cases studied bore no relationship to that following the operative procedure.

The study included eleven patients with essential hypertension, four with malignant hypertension, and one with chronic Bright's disease. Fourteen of the sixteen patients had appreciable reduction of blood pressure with the drug, as well as after the sodium amytal test. Twelve of these were operated upon, but only two of them had any significant change in resting supine blood pressure measurements two to four weeks after operation.

DURANT.

Breitwieser, E. R.: Electrocardiographic Observations in Chronic Cholecystitis Before and After Surgery. Am. J. M. Sc. 213:598 (May), 1947.

Preoperative and postoperative electrocardiographic studies in seventeen cases of calculous cholecystitis and one case of noncalculous cholecystitis are reported, all of the cases having had abnormal preoperative tracings. Including those with cardiac symptoms, as well as those with-

out, 50 per cent showed reversion of the T waves toward normal following gall bladder surgery. Exclusion of the five patients with hypertension did not significantly change this percentage. The author concludes that T-wave changes, unless associated with other indications of severe myocardial damage, should not be considered a contraindication to operation in chronic cholecystitis.

It should be added that the amount of T-wave change in the one set of tracings reproduced is very minimal.

DURANT.

Zeman, F. D., and Siegal, S.: Monoplegia Following Carotid Sinus Pressure in the Aged. *Am. J. M. Sc.* 213:603 (May), 1947.

A man, aged 83 years, with long-standing hypertension, developed a permanent right monoplegia within a few minutes after carotid sinus testing in the recumbent position. A review of the literature is presented and includes the observation of others that irreversible reactions to the cerebral type of carotid sinus hypersensitivity may occur. A warning is sounded against the casual employment of carotid sinus pressure either as a diagnostic test or therapeutic measure in aged patients suffering from hypertension and arteriosclerosis. It is suggested that the hypersensitive carotid sinus reflex may play a role in the precipitation of spontaneous cerebral accidents, and it is devised that aged patients, or even those over 50, with hypertension or arteriosclerosis be warned to avoid constriction of the neck, abrupt movements of the neck or head, straining at the stool, or heavy lifting and bending.

DURANT.

Kirk, G. D.: Ligation of Inferior Vena Cava for Septic Thrombophlebitis. *Am. J. Surg.* 73:606 (May), 1947.

The author presented a case of septic iliofemoral thrombophlebitis following reactivation of an old retropelvic infection associated with a gunshot wound of the right buttock and sacrum. When the infection could not be controlled by penicillin and, subsequently, by streptomycin, the inferior vena cava was ligated in an attempt to control the septicemia. Following this procedure there was moderate edema of both thighs, particularly the left, and of the back, which reached its maximal degree in the third day and subsided to practically normal by the eighth day. Despite the operation, the patient died of a suppurative meningitis.

ABRAMSON.

Shafiroff, B. J. P.: Ligation of the Inferior Vena Cava. *Am. J. Surg.* 73:621 (May), 1947.

A case is reported of a 22-year-old man who developed a pulmonary embolus seven days following an appendectomy for acute appendicitis. During the next two weeks a bilateral thrombophlebitis of both legs was observed. The patient was treated with sulfadiazine and oxygen, and later with penicillin and heparin. He was discharged as recovered after three months of hospitalization.

Three months later a new pulmonary embolus occurred, and shortly thereafter a thrombophlebitis of the right leg. Examination revealed, in addition, tenderness of both femoral veins and positive Homan's signs. Ligation of the inferior vena cava was carried out along with perivenous stripping of the vena cava and excision of the right third lumbar sympathetic ganglion. The postoperative course was uneventful and during the follow-up period of seven months the patient has remained entirely well, except for a twenty-four hour period of redness and tenderness of a superficial vein of the thigh.

The author concludes that ligation of the inferior vena cava is a sound operation and is indicated when a diagnosis of pelvic vein thrombophlebitis or bilateral phlebothrombosis of the lower extremities has been made.

LORD.

Davis, E.: Mitral Stenosis and Pulmonary Tuberculosis. *Am. Rev. Tuberc.* 55:457 (May), 1947.

This author reports that nearly 1 per cent of patients with active pulmonary tuberculosis had mitral stenosis. Among 725 patients with active pulmonary tuberculosis who had tubercle bacilli in their sputum, twenty-seven patients gave convincing evidence of rheumatic fever, and three others gave a history of chorea in childhood. Of the twenty-seven cases with evidence of rheumatic fever and tubercle bacilli in their sputum, six showed unequivocal signs of mitral stenosis. The remaining twenty-one patients, although they showed rheumatic mitral disease, did not have stenosis. During the period when these 725 patients with active tuberculosis were seen, 538 other patients were seen with convincing histories or signs of rheumatic fever or chorea. Of these, three developed lymphocytic pleural effusions, and three others stated that they developed active pulmonary tuberculosis from which they recovered.

BELLET.

Morton, J. J., Mahoney, E. B., and Mider, G. B.: An Evaluation of Pulmonary Embolism Following Intravascular Venous Thrombosis. *Ann. Surg.* 125:590 (May), 1947.

Morton and associates analyze their experience over the past twenty years at the Strong Memorial and Rochester Municipal Hospitals with venous thrombosis and pulmonary embolism. They found that most fatal emboli occur in surgical patients over 50 years of age and that there was no significant sex difference. One important factor in determining whether an embolus would prove to be fatal was the state of the heart. Patients with impaired circulation due to weakness of the cardiac muscle, valvular defect, and congestive failure were more susceptible to fatal embolization. The vast majority (80 per cent) of emboli occurred during the first two postoperative weeks.

The authors point out the position patients assume in bed and the degree of muscular activity while in bed are important in preventing venous thrombosis. The so-called "jack-knife" position impairs the venous return, whereas a relatively straight bed avoids this difficulty. Active exercises in bed are valuable, and early ambulation, when walking is practiced, is useful.

LORD.

Craig, W. M., and Abbott, K. H.: Surgical Considerations in the Treatment of Hypertension. *Ann. Surg.* 125:608 (May), 1947.

Hypertension is classified as (1) secondary, due to nephritis, urinary obstruction, and coarctation of the aorta, and (2) essential, or primary. The authors then grade hypertensive patients into four groups, employing Keith, Wagener, and Barker's definitions. From an analysis of their experience at the Mayo Clinic, Groups 1 and 2 (mild and moderate) are favorable for surgical intervention, whereas patients with advanced and fixed hypertension are less suitable.

The authors discuss briefly the various types of operations suggested for the lowering of the blood pressure and conclude that each one may be useful and have its place. The greatest problem remaining is the development of a test, or series of tests, for the selection of cases for surgical therapy.

LORD.

Walton, R. P., and Brodie, O. J.: The Effect of Drugs on the Contractile Force of a Section of the Right Ventricle Under Conditions of an Intact Circulation. Measurement of Isometric Systolic Tension By Means of Calibrated Springs Attached to Myo-Cardiograph Levers. *J. Pharmacol. & Exper. Therap.* 90:26 (May), 1947.

Small sutures were placed in the myocardium of the exposed right ventricle of dogs. These sutures were then connected with a calibrated myograph so arranged that a known force could be excited in the direction opposite to systole. Control figures for the amount of force necessary to abolish excursions of the recording lever during systole were first obtained on each specimen. Various drugs were administered in known quantities and the force necessary to abolish the sys-

tolic excursion noted. The results were expressed in percentage increase and decrease compared to the initial control.

Digitalis caused a constant increase in isometric contraction, averaging plus 37 per cent to plus 170 per cent. Epinephrine, likewise, showed a constant increase, averaging plus 225 per cent. Ephedrine, both in very small repeated doses and in single large doses, caused a constant increase. With repeated massive single doses there was a decrease in isometric contraction with cardiac dilatation.

EA-83 (2-methylamino-6-hydroxy-6-methyl heptane) produced a constant increase in strength of contraction, but blood pressure was not as markedly elevated as it was with epinephrine. Caffeine barium, calcium, and potassium salts all produced an increase in isometric contraction; quinidine and amyl nitrite produced a decrease.

The study of isometric systolic tensions may furnish a method of bioassay for cardiac drugs.
GODFREY.

Elkeles, A.: Disseminated Ossified Nodules in the Lungs Associated With Mitral Stenosis. *Proc. Roy. Soc. Med.* 40:405 (May), 1947.

The author describes a special type of pulmonary nodular calcification occasionally encountered in patients with mitral stenosis. He suggests that the ossified pulmonary nodules are the end result of rheumatic pneumonia and not, as hitherto believed, the outcome of long-standing passive congestion of the lungs in mitral stenosis.

Two cases of rheumatic heart disease with advanced mitral stenosis are reported which presented such calcifications. One of these came to necropsy. Microscopic examination of the nodules proved them to consist of bone of the woven type and intra-alveolar in position. The healed primary focus of tuberculosis can be distinguished from the ossified nodules in mitral stenosis by the destruction of the elastic framework of the affected area and by marginal calcification.

The author compares the radiologic appearance of pulmonary lesions of calcified miliary tuberculosis with those of the calcified nodules in mitral stenosis. In mitral stenosis the calcified nodules vary in size from pinhead to a large pea. They show various shades of density, are not always discrete, and have a tendency to coalesce. The nodules are distributed over the central lung fields, as well as the periphery. In calcified miliary tuberculosis the calcified nodules are discrete and more uniform in size and density. They mainly involve the central lung fields. There is usually evidence of primary or of post-primary tuberculosis lesions.

BELLET.

Eichna, L. W., Horvath, S. M., and Bean, W. B.: Post-exertional Orthostatic Hypotension. *Am. J. M. Sc.* 213:641 (June), 1947.

Transitory nonfatal collapse following severe physical effort is a familiar phenomenon in competitive sport. Observations dealing with the orthostatic hypotension, which is one of the circulatory aspects of this "Sportkrankheit," have been few, however. While studying the physiologic effects induced in healthy young men worked to the limits of their physical tolerance, the authors encountered postexertional orthostatic hypotension and had an opportunity to study it.

It was found that orthostatic hypotension developed in approximately one-half of the subjects following vigorous exercise of the lower extremities. It followed prolonged moderate work, as well as acute exhausting effort. In one-half of those who developed orthostatic hypotension (one-fourth of all subjects) the hypotension was so severe that syncope resulted. There was often a persistence of the orthostatic hypotension for periods longer than one hour after cessation of the inducing physical effort. The causative factor appeared to be a pooling of blood in the dependent lower extremities, presumably due to failure of the muscular venopressor mechanism in the legs, plus a work-induced dilatation of their vascular beds. During the orthostatic hypotension, maneuvers which move blood out of the lower extremities, or exclude blood from them, relieve the hypotension.

DURANT.

Odell, L. D.: Renal Filtration Rates in Pregnancy Toxemia; Inulin and Exogenous Creatinine. Am. J. M. Sc. 213:709 (June), 1947.

Simultaneous inulin, exogenous creatinine, and urea clearance tests were obtained from fifteen women, twelve of whom had severe signs of pregnancy toxemia. Urinary output, under identical conditions of fluid intake, improved markedly post partum. Results for urea clearance compared favorably with established standards. With few exceptions, figures for exogenous creatinine clearance exceeded those for inulin.

In severe pre-eclampsia, inulin, exogenous creatinine, and urea clearance rates were comparatively reduced ante partum, and improved during the puerperium. Considerable variation in inulin clearance values exists in patients with pregnancy toxemia.

Severe cases, particularly those with oliguria, cannot be accurately investigated by the usual methods employing collected urine specimens. Consequently, additional evidence is necessary to determine the exact mechanism of oliguria and anuria. The possible etiological significance of angiospasm is postulated, since transient oliguria has been produced experimentally by prolonged immersion of a limb in an ice water bath, and, in addition, arteriolar constriction has been detected by ophthalmoscopy during an ice water test.

DURANT.

Poppen, J. L.: Extensive Combined Thoracolumbar Sympathectomy in Hypertension. Surg., Gynec. & Obst. 84:117 (June), 1947.

Poppen describes a technique for the removal of the sympathetic chain from the fourth thoracic through the second lumbar ganglia, along with the great, lesser, and least splanchnic nerves. Exposure is obtained extrapleurally by resection of short medial segments of the seventh or eighth ribs and the eleventh rib. The pleura has been accidentally opened in five per cent of the operations. Every effort is made to remove in toto the chain, which is then photographed. In this way it is possible to correlate the occasional postoperative findings of areas of excessive sweating with the presence or absence of ganglia in the specimen. The operative mortality rate has been extremely low, only one postoperative death having occurred in 250 patients with essential hypertension.

LORD.

Slocum, H. C., Hoefflich, E. A., and Allen, C. R.: Circulatory and Respiratory Distress From Extreme Positions on the Operating Table. Surg., Gynec. & Obst. 84:1051 (June), 1947.

The authors have discussed the relation of position on the operating table to the physiology of respiration and circulation. The four factors which normally aid the venous return in raising the blood against gravity are: (1) the impetus given the blood by the contraction of the left ventricle, (2) the support of vein walls due to tonus of the abdominal and limb muscles, (3) the suction and force-pump action on the great veins produced by normal respiratory movements, and (4) the control of the caliber of the venocapillary vessels of the splanchnic area by vasopressor and capillary tonus mechanisms.

They point out how various positions commonly used in surgery influence unfavorably the above factors and also exert a deleterious effect on respiratory movements, both costal and diaphragmatic. The "jack-knife" position for hemorrhoidectomy, the steep Trendelenburg position for pelvic procedures, the elevated kidney and gall bladder rests, and the lithotomy position all produce unfavorable factors for good respiratory and circulatory balance. They show illustrative anesthetic charts to confirm the theoretical considerations. The authors suggest that the flat supine position is the best and that when other positions are necessary they be employed in moderate rather than extreme degrees.

LORD.

Turchetti, A., and Schirosa G.: La Registrazione Grafica della Pressione Venosa. Cuore e circolaz 30:109, 1946.

By means of a graphic method which permits continuous recording of venous pressure, the slow changes of the latter were investigated. These consist of: (a) respiratory variations, (b) variations due to changes of cardiovascular dynamics, and (c) variations caused by changes of the venous tonus.

A detailed study of the respiratory variations both in the small and large veins of either the superior or the inferior cava district permitted the observation of many interesting data which should be read in the original article.

The graphic record of the cardiovascular variations permitted their analysis and the study of their time relation with both the carotid and the jugular pulsations. The variations of pressure of the right auricle are transmitted to the peripheral veins; however, the waves are gradually damped and reveal various changes of amplitude and shape which are largely the result of the tension existing in the venous system.

The variations of venous tonus are slow (the oscillations last thirty to sixty seconds) and usually irregular; however, they may present periodic oscillations. They may differ in various veins or extend to the whole venous district. Simultaneous variations of the entire venous system were not observed.

LUISADA.

Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients With Chronic Pulmonary Disease and Various Types of Cardio Circulatory Disease. J. Clin. Investigation 25:639 (July), 1946.

Mean right auricular pressure in resting, recumbent normal subjects varied between $+$ and -2 millimeters of mercury. The pressure variations within the cardiac cycle ranged between 4 and 8 mm. Hg and corresponded closely to Wigger's description of intra-auricular events in the cardiac cycle. During quiet respiration, fluctuations in auricular pressure, while small, were detectable. Maximum right ventricular systolic pressure ranged between 18 and 30 mm. Hg, and averaged 25 millimeters of mercury. Right ventricular pulse pressure varied between 20.5 and 26.5 mm. Hg and averaged 22.5 millimeters of mercury. Right ventricular diastolic pressure was, at times, subatmospheric. The most representative right ventricular pressure curve contour consisted of a rapid systolic rise preceded frequently by a small wave representing auricular systole. At the peak of ventricular systole one or more low frequency oscillations appeared, and following closure of the pulmonic valve, there was usually a small, brief dip below the general level.

Among patients with lesions predisposing to pulmonary hypertension and right ventricular strain and in whom there was no evidence of right heart failure, there were none with elevated ventricular diastolic or auricular pressures. Five patients with therapeutic pneumothorax, two with fibrothorax, two post pneumonectomy, and five of nineteen with pulmonary fibrosis and emphysema exhibited pressures within normal limits. One with kyphoscoliosis, one with mitral stenosis and insufficiency, and fourteen of the group with pulmonary fibrosis and emphysema exhibited elevated ventricular systolic and pulse pressures.

When right heart failure was present ventricular diastolic and auricular pressures were abnormally high and the pressure pulse contours from the right heart and peripheral venous system exhibited characteristic peculiarities except when modified by tricuspid insufficiency. Neither the tracings typical of tricuspid insufficiency nor those characteristic of right heart failure permitted an etiological diagnosis.

A patient with the classical clinical picture of constrictive pericarditis displayed a normal ventricular systolic pressure, high mean auricular and ventricular diastolic pressures, and a low ventricular pulse pressure.

The right heart pressures of several patients with systemic arterial hypertension were within the confines of normal.

Controlled phlebotomy was accompanied by a significant reduction in right ventricular pressures, which returned rapidly to normal following infusion of gelatin solution.

FRIEDLAND.

Cook, C. D., Smith, H. L., Giesen, C. W., and Berdez, G. L.: Xanthoma Tuberosum, Aortic Stenosis, Coronary Sclerosis and Angina Pectoris. Am. J. Dis. Child. 73:327 (March), 1947.

Thannhauser's classification divides primary xanthomatosis into two subgroups: the hypercholesterolemic, and the normocholesterolemic type. In the hypercholesterolemic type xanthoma of the tendons and tendon sheaths, xanthoma tuberosum, and xanthoma planum of the skin, xanthomatosis of the bile ducts with secondary jaundice and biliary cirrhosis, cardiovascular involvement, and scattered nests of xanthoma cells in the spleen, liver, and lymph nodes occur. In the normocholesterolemic type xanthoma disseminatum of the skin, mouth, and larynx, osseous involvement of the skull, scapula, pelvis, extremities, and orbits, xanthomatous involvement of the pituitary gland and tubercle of Rolando with diabetes insipidus, involvement of the brain, medulla, dura, lungs, and pleura, and scattered nests of xanthoma cells in the spleen, liver, and lymph nodes, as in the hypercholesterolemic type, occur. The case presented in this paper is typical of the hypercholesterolemic type because of the cardiac features and xanthoma tuberosum of the skin and xanthoma of the tendons.

The cause of primary xanthomatosis is not known, but Thannhauser has suggested that it is a disease of reticular cells caused by intracellular disorder of cholesterol metabolism. A review of twenty such cases taken from the literature revealed that all were 31 years of age, or less, and that all had definite or probable heart disease. Coronary disease and angina pectoris are common among patients with xanthoma tuberosum, and in the three autopsy cases that have been reported, all were found to have xanthomatous infiltration of the coronary arteries, aorta, and large arteries.

The patient herein described was a 13-year-old boy who had begun to develop soft, fluctuant, yellowish-pink, circumscribed tumors on the elbows, knees, ankles, joints of the fingers and toes, and buttocks. For six to eight months before admission the patient had had dyspnea and substernal pain on exertion. A systolic murmur with its maximal intensity over the aortic area was heard. This murmur was transmitted to the large vessels of the neck and was heard in the back as well. It was thought that the aortic systolic murmur was due to aortic stenosis and that the aortic stenosis was caused by xanthomatous infiltration of the aorta and aortic valves. The blood cholesterol was 561 mg. per 100 c.c.; cholesterol esters, 360 mg.; total fatty acids, 948 mg.; and total lipids, 1,509 milligrams. The level of blood lecithin was 496 mg. per cent. An electrocardiogram taken at rest showed a rate of 86 per minute with isoelectric T waves in Lead II and inverted T waves in Leads III, IVR, and IVF. During an attack of severe substernal pain the rate was 129, and there was considerable depression of the S-T segments in Leads I and II and even more depression in Leads IVR and IVF. The patient was eventually discharged from the hospital and one year later died rather suddenly. Autopsy examination was permitted and the findings confirmed the previous clinical impression. Grade 3 coronary sclerosis with pronounced narrowing of the anterior descending branch of the coronary artery was found, along with a beginning anemic infarct of the lower half of the anterior wall of the left ventricle. The cusps of the aortic valve were thickened and fibrous, and there was some hypertrophy and dilatation present. Microscopically, there were large deposits of fatty material in the myocardium and also in the intima of the coronary arteries.

HAUB.

Downing, M. E.: Blood Pressure of Normal Girls from Three to Sixteen Years of Age. Am. J. Dis. Child. 73:293 (March), 1947.

This article includes a review of the literature and a discussion of various factors that influence blood pressure in young persons, such as age, height, weight, posture, and the width of the cuff used. The purpose of this study was to find the normal blood pressures, using both the child and the adult cuffs, for the same girls who were followed from early childhood into adolescence,

and to find the age or size at which it is best to change from the child to the adult cuff. Weight did not seem very important.

The data presented indicates that height best indicates when to change from the child cuff to the adult cuff. This height is probably in the range of 50.00 to 53.99 inches. The pressure in any one child varies considerably from day to day and even from year to year. In some children there was even a decrease from one year to the next. The most important thing is to know the normal range of blood pressure with the cuff used for the given age and size of child in question, and to know when the child varies from his own normal or from the normal range for his size. If the cuff used for the child is about the same width, in proportion to the size of his arm, as the adult cuff is to the size of the average adult arm the readings are probably comparable.

HAUB.

Wedding, E. S.: Actinomycotic Endocarditis. Arch. Int. Med. 79:203 (Feb.), 1947.

The literature on bacterial endocarditis due to higher forms of bacteria is reviewed and discloses four cases in which there was a clinical picture without evidence of a portal of entry. In one of the cases reported, inoculation of a rat by a special technique produced pathologic evidence of infection with *Actinomyces*, and the organism was recovered in pure culture from the inoculated animal. Coccal structures, rods, filaments, and branching filaments were observed in vegetations of the aortic valve in the other case, in which an aerobic strain of *Actinomyces* was recovered from the valves, but, in the opinion of the author, contaminants were present in the original culture.

Careful laboratory procedures are the only way in which this diagnosis can be made and differentiated from subacute bacterial endocarditis due to *Streptococcus viridans*.

HORWITZ.

Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever. Am. J. M. Sc. 213:482 (April), 1947.

The author has confirmed recently reported observations that salicylates may lower the erythrocyte sedimentation rate of nonrheumatic as well as of rheumatic patients. Hence the erythrocyte sedimentation rate may not be relied upon as a criterion of improvement in inflammatory reaction in rheumatic fever. The hypothesis that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient was tested by treating in this way patients in whom the rheumatic process was so active as to produce a prolonged leucocytosis. It was found that, although the erythrocyte sedimentation rate is lowered to normal limits by such treatment, the leucocytosis may remain, although the latter is a much less sensitive indicator of inflammation. This finding is supported by a continued shift to the left in the differential blood count, and by specific signs of continued rheumatic activity which were observed while the erythrocyte sedimentation rate was within normal limits as a result of salicylate treatment. It is doubtful, therefore, that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient or that the lowering of the erythrocyte sedimentation rate in rheumatic patients so treated has the significance attributed to it by Coburn.

DURANT.

Book Reviews

CARDIOVASCULAR DISEASES. David Scherf, M.D., and Linn J. Boyd, M.D., J. B. Lippincott Company, 1947, Philadelphia. With 478 pages, 31 chapters, and 56 illustrations.

The authors state in the preface to this edition of their book that they decided to rewrite it completely and that "In place of a series of essays on selected cardiac problems, a more detailed discussion of cardiovascular diseases is presented in this new volume."

Certain subjects, incompletely considered in previous editions, have been more fully covered, such as rheumatic fever, irradiation of autonomic reflexes, and arteriovenous anastomoses; and the material on others, including roentgenology, myocarditis, and newer therapies, has been expanded.

The book, however, still retains the structure of a series of lectures without any obvious system. The first chapter, for example, is on dyspnea, and the sixteenth chapter is on anginal pain and its differential diagnosis, directly after a chapter on congenital cardiovascular defects. Constant reliance, therefore, on the extensive index is necessary to collect all the information on a single subject. References to the literature, much of it in German, are placed at the end of each chapter and add considerably to the value of the book.

The physiologic discussions, as in the chapters on dyspnea, and compensation and decompensation, are good expositions and cover modern literature satisfactorily. The cardiac manifestations of endocrine disease, especially those in ovarian dysfunction, may not be considered by others to be as specific as they seem to be to these authors, who believe, for example, that sighing respiration on the basis of ovarian hypofunction is "a common and regular finding." It is also stated that "about 22 per cent of all women coming to a cardiologist for advice have complaints referable to disturbance of activity of the ovaries."

In the consideration of mitral stenosis the authors state that the presystolic murmur is the first one to appear in the usual development of this lesion, and relate it to the increased velocity of the blood with auricular contraction. It is the experience of the reviewer that the mid-diastolic murmur occurring during the rapid inflow stage of ventricular filling is more often the herald of beginning stenosis, even though it may be, for a time, indistinguishable from the murmur of left ventricular dilatation in active rheumatic carditis. One notes, also, no discussion of hemoptysis as a complication of mitral stenosis.

The relatively little attention given to electrocardiography is intentional, as this lack has been supplied by the authors in their companion volume on Clinical Electrocardiography.

Recommendations for therapy conform in general to the accepted procedures. It may be noted, however, that the use of leeches over the liver in acute congestion and over the veins in painful thrombophlebitis is still defended. It is wisely pointed out that the bradycardia of aortic stenosis and of complete heart block should not preclude digitalis therapy when otherwise indicated. As one of the causes of the small left ventricle in mitral stenosis, the limitation of physical effort by dyspnea is cited, and it is recommended that patients should be encouraged to continue exercise which does not produce symptoms to prevent this atrophy of the heart.

Aminophylline suppositories are advised as the "safest and most gratifying" therapy for heart block with Adams-Stokes attacks, but the authors warn against theobromine, caffeine, and theophylline in patients in whom the danger of thrombosis exists, due to their effect in causing hyperthrombinemia. Combining ephedrine and barium chloride in heart block is considered dangerous, as it will often evoke ventricular fibrillation.

The authors' interest in myocarditis re-emphasizes a subject worthy of consideration, especially in view of recent evidence of virus injury to heart muscle, as in primary atypical pneu-

monia and mumps. They repeat the assertion of earlier editions that "only a few individuals completely and permanently escape small inflammatory foci in the myocardium (myocarditis)."

There is a full consideration of coronary artery disease in the chapter on anginal pain. It is emphasized that in the examination of elderly individuals prior to operation "it is safer to state that the examination does not disclose coronary sclerosis than to say that coronary sclerosis is absent."

With myocardial infarction, "pericarditis, in general, represents a desirable complication, for the local inflammation speeds the healing process."

The occurrence of a deep Q wave in Lead I in the electrocardiogram of patients who once had a myocardial infarction supports a suspicion of cardiac aneurysm.

Dupuytren's contracture, as well as the more common painful shoulder, may follow myocardial infarction.

Peripheral vascular disease is covered in a forty-four page section, and the final chapter of thirty-nine pages is concerned with therapy.

The knowledge of cardiovascular disease is brought well up to date in this volume. The few omissions are dependent upon the present velocity of the stream of information concerning circulatory disorders. The great value of venous catheterization of the heart in the diagnosis of congenital heart disease is not mentioned. Ligation and division, which has in the main replaced simple ligation of the patent ductus, is also omitted, as is the very recent operation of anastomosis of aorta and pulmonary artery in certain congenital cardiovascular defects associated with cyanosis. The newer concepts concerned with fluid retention and sodium excretion mechanisms in congestive failure are not emphasized to the degree that seems at present justified.

It is recommended that this book be read in its entirety to obtain a useful review of cardiovascular physiology, diagnosis, and treatment. It does not cover the field of electrocardiography, but with a total of 1,984 references to literature on the circulation, it can well serve as a bibliography of the general field of diseases of the heart and blood vessels.

HOWARD B. SPRAGUE.

LE FORME CLINICHE ATIPICHE DELL'INFARTO MIocardico. By Iandolo, C., Edizioni Scientifiche Italiane, Naples, Italy, 1946, with 102 pages.

This monograph deals with cases of myocardial infarction which have an atypical clinical picture. Following a scheme which reminds one of the traditions of the French school, the author describes: (1) Infarctions with few clinical signs (so-called mild cases). (2) Infarctions where one clinical sign (pain, fever, collapse, or dyspnea) is predominant. (3) Infarctions with an atypical picture in which various abdominal, respiratory, or metabolic syndromes may be simulated. The study of Iandolo is based on personal observation of twenty-two atypical cases out of a series of 165 cases of infarction (13.3 per cent). The discussion is supplemented by brief reports of all the atypical cases.

While the book does not add to what is already known, it may emphasize the need for a more detailed consideration of the atypical and mild types of myocardial infarction.

A. LUISADA.

DIAGNOSTIC ELECTROCARDIOGRAPHIQUE. By André Jouve, Jaques Senez, and Jean Pierron, Masson & Cie, Paris, 1946, with 336 pages and 217 illustrations.

This volume, it appears, represents the first textbook on electrocardiography in France, and therefore is destined to assume an authoritative position in the European literature. The text is sound and conservative and is conventionally divided into four sections. A discussion of basic theories and techniques is followed by a section dealing with the normal variations of the electrocardiographic curve, which includes a chapter on the theoretical interpretation of such records. The third part comprises a section on the abnormal electrocardiogram and cardiac arrhythmias. The fourth section attempts to correlate electrocardiographic patterns with certain diseases, drug actions, and clinical syndromes.

The reviewer finds that the wealth of factual material presented often overshadows the basic principles necessary for understanding and interpretation of an electrocardiogram. The

spread of the action current over auricular and ventricular muscle, as traced and analyzed by many workers, has a direct bearing on the form and shape of any electrocardiographic lead. Familiarity with the laws which govern the distribution of currents in conductors such as the heart is of far more direct benefit to the student than the memorizing of certain patterns. Yet, in texts of this sort, such basic information is usually treated in small print as a necessary evil rather than as a foundation upon which to base the teaching of clinical electrocardiography. Similarly, the use of precordial or esophageal leads is treated as an additional new subject rather than as an integral part bridging the way from experimental curves obtained from endocardial and epicardial surfaces to unipolar and bipolar limb leads. The lack of such integration results in the accumulation of empirical facts rather than in a logical explanation of the abnormal electrocardiogram in myocardial infarction, bundle branch block, extrasystoles, and similar abnormalities. On the other hand, too much emphasis is perhaps placed on the calculation of the direction of the electrical axes which are of limited value in clinical electrocardiography. The extension of Einthoven's theorems to include important concepts, such as the calculation of the area of electrocardiographic deflections and the ventricular gradient, receive scant attention indeed.

The difficulties under which this book must have been written explains perhaps some of its defects, although much of this information was known to, and published by, European investigators before the war. This probably accounts also for the peculiar nomenclature and adherence to the earlier methods of recording precordial leads in which a positivity of the exploring electrode was represented by a downward deflection. This will undoubtedly revive some of the earlier confusion. The new method reversing the original polarity was common usage in Germany, Switzerland, and the Scandinavian countries before its universal acceptance in the United States, Great Britain, and South America.

The fundamental criticism which must be stressed is one that may be made for all but a few texts on the subject. This book compares very favorably with others in presenting the results of experimental and empirical information. The attempt to correlate clinical syndromes with electrocardiographic patterns, to which one-fourth of the book is devoted, is an extremely difficult one and is handled sparingly and with great reservation. One would wish that in future editions this section would be expanded and perhaps more profusely illustrated. It is one to which the beginner as well as the clinician familiar with the subject matter will turn to most readily. In its present form this section will leave many questions unanswered.

As it stands, the book has great merits and will undoubtedly receive the credit it really deserves. It is beautifully written, easily understood, and impeccably set to type. The illustrations, which are often accompanied by sound records, are well selected and in the main are excellently reproduced.

H. H. HECHT.

LA DIGITALE ET LES STROPHANTINES. PHARMACODYNAMIE—THERAPEUTIQUE. By D. Danielopolu, Bucharest. Masson & Cie Editeurs, Paris, 1946. With 206 pages and 56 illustrations.

Danielopolu, who occupied himself with the physiology and pharmacology of the vegetative nervous system for thirty years, in his new book on digitalis and strophanthines presents his views on the action of digitalis and allied drugs. These views are based on his experimental studies and clinical observations, and stem from his personal interpretation of the vegetative system.

Digitalis has no effect on the heart nerves and, in therapeutic doses, exerts no influence on the myocardium. Its action is achieved by its effect on both acetylcholine and sympathin: by inhibiting the cholinesterase (antiacetylcholinolytic effect) it protects acetylcholine from being hydrolysed; simultaneously, it intensifies the effectiveness of sympathin. Since mediators of both systems are always influenced, digitalis is called "amphotropic with predominant effect on one or the other component."

Digitalis in large doses has a "specific" (toxic) effect on the heart muscle; the cell plasma is damaged irreversibly. In therapeutic doses, the "nonspecific" effect is brought about: the drug produces augmentation of irritability, contractility, and tonicity through enhancing the action

of sympathin on the adult type of fibers; whereas the inhibiting effect of the same dose on rhythmicity and conductivity is attributed to its acetylcholinergic action on the embryonic type of fibers.

In addition to the usual indications, digitalis is recommended for the treatment of essential hypertension ("the best hypotensive drug we possess") and angina pectoris. The acetylcholine spared from lysis will produce a hypotensive effect by its action on small vessels. Anginal attacks are prevented by the lowered blood pressure, by the augmented myocardial blood flow of a lengthened diastole, and by an increase of myocardial resistance against fatigue.

Danielopolu is an ardent advocate of strophanthin. He uses it in intramuscular injections and considers it the drug of choice in acute myocardial insufficiency of infectious origin and in chronic heart failure complicated by a febrile disease. Strophanthin is occasionally effective when digitalis fails.

The book also contains a chapter on the history of the use of digitalis, as well as one giving a very exhaustive presentation of the author's theory of the function of the vegetative system.

The section dealing with digitalis and the electrocardiogram appears simply at odds with facts.

An outstanding feature of the book is its lively style. Although the points of view on the action of digitalis, as exposed, differ from those accepted in this country, it cannot be denied that they have been brought into a unified system harmonizing with the author's conception of vegetative physiology.

The absence of a table of contents and of an alphabetical index makes the orientation in the text rather difficult. The print is poor and typographical errors abound.

J. BRUMLIK.

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

The Chairman of the Program Committee for the Annual Scientific Session is Dr. Herrman L. Blumgart, 330 Brookline Avenue, Boston, Massachusetts. All who desire to present papers at the meetings in Chicago on June 18 and 19 should forward to Dr. Blumgart an abstract of the proposed presentation of not more than 500 words. The dead line for the receipt of abstracts is Feb. 1, 1948.

MEMBERSHIP

The American Heart Association and its local affiliates throughout the United States have agreed upon a system of interrelated membership. New members residing in areas where local Heart Associations exist shall be joint members of both the local and the American Heart Association. New members resident in areas where no local affiliated Heart Association exists may apply directly for membership. In addition to physicians, members of other professional groups and laymen are now welcome as members of the American Heart Association.

Membership blanks will be sent upon request, as well as information about membership in local Heart Associations. The following types of membership are provided by the American Heart Association.

Annual Membership.....	\$ 2.50	Contributing Membership.....	\$25.00
Journal Membership.....	\$10.00	Patron Membership.....	\$50.00 or more

The dues of the local Heart Associations are added to these.

Annual Membership includes twelve issues of *Modern Concepts of Cardiovascular Disease*

Journal Membership includes a year's subscription to the AMERICAN HEART JOURNAL (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease* and annual membership in the Association. (A special Journal Membership for the remainder of 1947 is available for a limited time. Details will be given on request.)

Subscription to the AMERICAN HEART JOURNAL through the publishers does not provide for membership in the American Heart Association, except as provided for in a Journal Membership.

THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

OFFICERS

President
DR. ARLIE R. BARNES

Treasurer
SAMUEL HARRELL

President Elect
DR. TINSLEY R. HARRISON

Secretary
DR. HARRY E. UNGERLEIDER

Medical Director
DR. CHARLES A. R. CONNOR

Vice-President
DR. CARL J. WIGGERS

Executive Secretary
DR. H. M. MARVIN

BOARD OF DIRECTORS

*THOMAS I. PARKINSON, Chairman..... New York City
DR. EDGAR V. ALLEN..... Rochester, Minn.
*DR. E. COWLES ANDRUS..... Baltimore
*DR. ARLIE R. BARNES..... Rochester, Minn.
DR. WILLIAM H. BURN..... Youngstown, Ohio
*DR. GEORGE E. BURCH..... New Orleans
*S. DEWITT CLOUGH..... Chicago
*COLGATE W. DARDEN, JR..... Charlottesville, Va.
*JUSTIN DART..... Los Angeles
DR. CLARENCE E. DE LA CHAPELLE..... New York City
DR. GEORGE K. FENN..... Chicago
DR. MORRIS FISHBEIN..... Chicago
RUDOLPH F. HAFENREFFER..... Providence
*SAMUEL HARRELL..... Indianapolis
*DR. TINSLEY R. HARRISON..... Dallas
ALFRED C. HOWELL..... Bethel, Conn.
*DR. T. DUCKETT JONES..... Boston
DR. LOUIS N. KATZ..... Chicago

DR. JOHN D. KEITH..... Toronto, Can.
DR. ROBERT L. KING..... Seattle
MRS. WENDELL KINNEY..... Los Angeles
DR. WILLIAM B. KOUNTZ..... St. Louis
DR. EUGENE M. LANDIS..... Boston
DR. ROBERT L. LEVY..... New York City
DR. H. M. MARVIN..... New Haven, Conn.
DR. THOMAS M. McMILLAN..... Philadelphia
*ROBERT L. MEHORNAY..... Kansas City, Mo.
*DR. IRVINE H. PAGE..... Cleveland
*DR. JOHN J. SAMPSON..... San Francisco
DR. HOWARD B. SPRAGUE..... Boston
DR. EUGENE A. STEAD, JR..... Durham, N. C.
DR. J. ROSS VEAL..... Washington, D. C.
DR. HARRY E. UNGERLEIDER..... New York City
DR. HOWARD F. WEST..... Los Angeles
DR. CARL J. WIGGERS..... Cleveland
*DR. IRVING S. WRIGHT..... New York City

*Executive Committee.

ASSEMBLY

DR. EDGAR V. ALLEN..... Rochester, Minn.
JAMES ANDERSON..... Philadelphia
DR. E. COWLES ANDRUS..... Baltimore
DR. GRAHAM ASHER..... Kansas City, Mo.
DR. ARLIE R. BARNES..... Rochester, Minn.
DR. EMMET B. BAY..... Chicago
DR. ALFRED BLALOCK..... Baltimore
ALVA BRADLEY..... Cleveland
EARLE BROWN..... Minneapolis
DR. LEWIS T. BULLOCK..... Los Angeles
DR. WILLIAM H. BURN..... Youngstown, Ohio
DR. GEORGE E. BURCH..... New Orleans
DR. EDWARD W. CANNADY..... East St. Louis, Ill.
HARRY C. CARR..... Philadelphia
DR. FRANCIS L. CHAMBERLAIN..... San Francisco
PAUL F. CLARK..... Boston
S. DEWITT CLOUGH..... Chicago
DR. WARREN B. COOKSEY..... Detroit
CHANNING H. COX..... Boston
JAMES A. CUNNINGHAM..... Chicago
COLGATE W. DARDEN, JR..... Charlottesville, Va.
JUSTIN DART..... Los Angeles
DR. CLARENCE E. DE LA CHAPELLE..... New York City
DR. GEZA DE TAKATS..... Chicago
DR. FRANCIS R. DIEUAIDE..... New York City
DR. HARVEY M. EWING..... Montclair, N. J.
DR. GEORGE K. FENN..... Chicago
RICHARD J. FINNEGAN..... Chicago
DR. MORRIS FISHBEIN..... Chicago
DR. NORMAN E. FREEMAN..... San Francisco
ARTEMUS L. GATES..... New York City
SAMUEL GOLDWYN..... Los Angeles
A. E. GRAUER..... Vancouver, B. C., Can.
DR. JAMES A. GREENE..... Houston
RUDOLPH F. HAFENREFFER..... Providence
SAMUEL HARRELL..... Indianapolis
RICHARD F. HARRISON..... Syracuse, N. Y.
DR. TINSLEY R. HARRISON..... Dallas
DR. JOHN HEBURN..... Toronto, Can.
DR. GEORGE R. HERMANN..... Galveston
DR. J. G. FRED HISS..... Syracuse, N. Y.
ALFRED C. HOWELL..... Bethel, Conn.
DR. W. C. HUEPER..... New York City
COLEMAN JENNINGS..... Washington, D. C.
DR. T. DUCKETT JONES..... Boston
DR. ALBERT D. KAISER..... Rochester, N. Y.
DR. LOUIS N. KATZ..... Chicago
SAMUEL H. KAUFFMANN..... Washington, D. C.
DR. JEROME G. KAUFMAN..... Newark, N. J.
DR. JOHN D. KEITH..... Toronto, Can.
DR. ROBERT L. KING..... Seattle
MRS. WENDELL KINNEY..... Los Angeles
DR. WILLIAM B. KOUNTZ..... St. Louis
DR. CHESTER M. KURTZ..... Madison, Wis.
DR. EUGENE M. LANDIS..... Boston

DR. BERNARD W. LEONARD..... Washington, D. C.
DR. ROBERT L. LEVY..... New York City
CLARE BOOTHE LUCE..... Ridgefield, Conn.
DR. HAROLD C. LUETH..... Omaha
RUTH E. LYNCH..... Los Angeles
DR. LOUIS E. MARTIN..... Los Angeles
DR. H. M. MARVIN..... New Haven, Conn.
DR. EDWIN P. MAYNARD, JR..... Brooklyn
DR. SAMUEL J. MCCLENDON..... San Diego
ALFRED J. MCCOSKER..... New York City
DR. HUGH MCCULLOCK..... St. Louis
DR. JOHNSON MCGUIRE..... Cincinnati
DR. THOMAS M. McMILLAN..... Philadelphia
ROBERT L. MEHORNAY..... Kansas City, Mo.
DR. J. ROSCOE MILLER..... Chicago
RICHARD M. MOSS..... Belleville, Ill.
DR. E. STERLING NICHOL..... Miami
DR. FRANKLIN R. NUZUM..... Santa Barbara, Calif.
DR. IRVINE H. PAGE..... Cleveland
THOMAS I. PARKINSON..... New York City
DR. MYRON PRINZMETAL..... Los Angeles
DR. SAMUEL PROGER..... Boston
DR. DICKINSON W. RICHARDS, JR..... New York City
DR. HAROLD H. ROSENBLUM..... San Francisco
DR. PHILIP ROSENBLUM..... Chicago
DR. HOMER P. RUSH..... Portland, Ore.
DR. JOHN J. SAMPSON..... San Francisco
DR. FRANCIS T. SCHWENTKER..... Baltimore
DR. HAROLD N. SEGALL..... Montreal, Can.
DR. ARTHUR SELZER..... San Francisco
DR. M. J. SHAPIRO..... Minneapolis
DR. HOWARD B. SPRAGUE..... Boston
DR. ISAAC STARR..... Philadelphia
HAROLD E. STASSEN..... St. Paul
DR. EUGENE A. STEAD, JR..... Durham, N. C.
DR. ERNEST L. STERRINS..... Baltimore
DR. WILLIAM D. STROUD..... Philadelphia
DR. HOMER F. SWIFT..... New York City
DR. ALEXANDER W. TERRELL..... Dallas
DR. WILLIAM P. THOMPSON..... Los Angeles
DR. HARRY E. UNGERLEIDER..... New York City
DR. J. ROSS VEAL..... Washington, D. C.
DR. LOUIS E. VIKO..... Salt Lake City
DR. MAURICE VISSCHER..... Minneapolis
JOE E. WERTHAN..... Nashville
DR. HOWARD F. WEST..... Los Angeles
DR. PAUL D. WHITE..... Boston
CARL WHITMORE..... New York City
DR. CARL J. WIGGERS..... Cleveland
DR. FRANK N. WILSON..... Ann Arbor
DR. J. EDWIN WOOD, JR..... Charlottesville, Va.
GUS S. WORTHAM..... Houston
DR. IRVING S. WRIGHT..... New York City
J. D. ZELLERHACH..... San Francisco



American Heart Journal

VOL. 34

DECEMBER, 1947

No. 6

Original Communications

NORMAL VARIATIONS IN MULTIPLE PRECORDIAL LEADS

GORDON B. MYERS, M.D., HOWARD A. KLEIN, M.D.,
BERT E. STOFER, M.D., AND TOMIHARU HIRATZKA, M.D.
DETROIT, MICH.

ALTHOUGH precordial leads have been used clinically for fifteen years, there is still no general agreement as to the minimal number of leads necessary for an adequate examination. The advisability of multiple precordial leads was early emphasized by Wilson and associates as a result of their experience with direct leads in animals¹⁻³ and in the exposed human heart,⁴ and has been supported by a vast amount of clinical data, not only from the Wilson group⁵ but also from many other sources. Nevertheless, there is lack of extensive studies correlating findings in multiple precordial leads with those at necropsy. This may in part account for the fact that many cardiologists, perhaps the majority, are still content with a single precordial lead.

To fulfill an apparent need, a comprehensive study correlating electrocardiographic and autopsy findings was commenced in 1941 and is still in progress. To date 1,000 cases in which multiple precordial leads were taken during life have been followed to necropsy.* In 439 of these, post-mortem examination included injection of the coronary arteries with radiopaque mass, roentgenogram, and subsequent dissection with multiple microscopic blocks. The data obtained through the electrocardiographic-autopsy correlations will form the basis for a series of papers.

From the Departments of Medicine and Pathology of Wayne University, and City of Detroit Receiving Hospital.

Received for publication Feb. 27, 1947.

*We are greatly indebted to Dr. S. E. Gould, Pathologist at Wayne County General Hospital, for permission to make free use of his autopsy files on cases we previously had studied electrocardiographically.

GENERAL PROCEDURE

Electrocardiographic Study.—The central terminal of Wilson and co-workers⁶ has been employed throughout this study in order to minimize the influence of the indifferent electrode, and thereby obtain as accurate a record as possible of the potential variations of the exploring electrode. When the remote electrode is connected to all three extremities through the central terminal, its potential variations are reduced to an almost negligible quantity which at the most does not exceed 0.3 millivolt.⁷⁻⁹ On the other hand, when the remote electrode is applied to a single extremity its potential variations are subject to a much wider range, depending upon cardiac position and other factors, and are often large enough to distort the recordings from the precordial electrode, as shown by the significant differences in the pattern obtained by CR, CL, and CF leads.¹⁰ More recently, Wolferth and associates¹¹ have criticized the central terminal and have advocated application of the remote electrode to the spine of the right scapula. However, the potential variations in this region usually correspond to those of the right arm and precordial leads obtained with the remote electrode on the spine of the scapula closely resemble the CR leads.¹² Thus, the central terminal appears preferable to any arrangement in which the remote electrode is applied to a single point.

At the beginning of this project the routine electrocardiogram in this laboratory included merely the standard limb leads and precordial Leads V_2 , V_4 , and V_6 . As the study progressed it became evident that leads from all six standard precordial reference points were advisable as a routine and that additional leads to the right, to the left, or above the customary positions were indicated under special circumstances. Furthermore, it was found that the augmented unipolar limb leads of Goldberger¹³ yielded valuable information regarding the portion of the heart resting on the diaphragm¹⁴ and that facing each arm, and have aided considerably in the analysis of the standard extremity leads. As a consequence, all electrocardiograms taken in this laboratory since 1943 have comprised Leads I, II, III, aV_R , aV_L , aV_F , V_1 , V_2 , V_3 , V_4 , V_5 , and V_6 . More recently Lead V_{3R} has been added to the routine, because of the information yielded in the diagnosis of right ventricular lesions.¹⁵

All tracings have been taken with the Cambridge mobile unit. To expedite the task of the technician, the electrocardiograph has been equipped with a multiple lead switch* constructed on the principle described by Ethridge and Stolar.¹⁶ The switch has an outlet wire for each of the three extremities and a fourth outlet wire permanently connected to the precordial electrode. The standard and Goldberger limb leads and Wilson precordial leads may be taken successively merely by moving the dial of the multiple lead switch without disturbing the connections to the patient. The switch is constructed so that the Wilson lead and each of the Goldberger leads may be taken with or without the inclusion of a 5000 ohm resistance in every connection of the indifferent electrode. The resistance is always advisable to minimize current flowing through the skin.¹⁷

*The multiple lead switch used in this laboratory was constructed by Mr. L. A. Boulet, Detroit, Mich.

Method of Pathologic Study.—The heart was removed by transection of the great vessels at their exit from the pericardium. The radiopaque mass used for injection of the coronary circulation consisted of a lead acetate-agar mixture.¹⁸ At the outset of the study, differently colored mixtures were injected simultaneously into the right and left coronary arteries under controlled pressures according to the technique of Schlesinger.¹⁸ This method of injection was time consuming and, in our experience, often failed to fill portions of the coronary tree which subsequently proved to be patent. Since our chief interest lay in the accurate localization of myocardial rather than coronary lesions, the roentgenogram of the injected heart was employed more as a map on which the position of lesions detected by gross or microscopic examination could be plotted. For our purposes, it was desirable to outline all grossly visible ramifications of the coronary tree that were not occluded by an adherent thrombus or plaque.

In order to simplify the procedure to a point where it could be used routinely, the injection technique was modified as follows: The cannulated left and right coronary arteries were injected successively with a warm uncolored lead agar mass from a hand syringe, using a pulsatile movement of the plunger. The injection was continued until the vessel was visibly distended or a resistance was encountered, whereupon the cannula was removed and a ligature tightened.

Injection from a syringe generally filled all grossly visible branches of the coronary arteries except the first branch of the right coronary which supplies a portion of the anterior aspect of the right ventricle. It was usually necessary to insert the cannula beyond the orifice of this branch in order to secure it firmly in place. Occasional failures to fill other patent branches, especially the posterior descending coronary artery, were encountered, but were much less common than with the Schlesinger technique of injection. It must be realized that injection from a syringe may dislodge ante-mortem thrombi that were not firmly adherent to the walls of a coronary artery and, therefore, may render visible portions of the coronary tree that were obstructed prior to death. It is also evident that the hearts injected by the syringe technique were not suitable for a reconstruction of the distribution of the right and left coronary circulation during life or for an evaluation of the direction of flow in anastomotic channels. These limitations of the syringe technique did not detract from the chief objective of this study, which was to correlate electrocardiographic findings with gross and histologic changes in the myocardium.

The heart was refrigerated overnight to harden the injection mass before sectioning. A modified Klotz solution¹⁹ was used as a preservative, in order to minimize color change and shrinkage. The Schlesinger method of sectioning,¹⁸ used in our first 167 cases, allows an unrolling of the cone-shaped heart so that both ventricles and the entire coronary tree are laid out flat for roentgenography. Although this is well adapted for the study of the coronary tree, it has two serious drawbacks from the standpoint of fulfilling our purposes, namely: (1) the roentgenogram gave no help in locating the position of lesions with reference to the endocardial or epicardial surface, since the entire thickness of myocardium was superimposed on the film; (2) the roentgenogram gave no help in

tracing the continuity of lesions from the anterior or posterior walls into the septum, since the latter was removed in the process of sectioning.

To overcome the disadvantages of the Schlesinger technique of opening the heart, a method of sectioning into transverse slices was substituted. The ventricles were first separated from the atria at the valvular ring by a transverse section parallel with the atrioventricular groove. The ventricles were then cut into a series of transverse slices 1 cm. thick.²⁰ These slices were placed on a cassette so that in the finished roentgenogram the apical segment was located in the upper left hand corner and intervening segments were arranged in rows from left to right and from above downward, ending with the most basal segment in the lower right hand corner. Each slice was placed so that the anterior surface of the ventricles was uppermost and the lateral walls of the left and right ventricles faced the left and right edges of the film, respectively. This method was used for the last 272 cases and proved more suitable for our purposes than the Schlesinger method of opening the heart.

The electrocardiographic diagnosis was made prior to the examination of any autopsy material. A careful gross examination of each transverse slice was made in conjunction with the roentgenogram of the injected heart and with knowledge of the electrocardiographic findings. The exact location of gross lesions was drawn on the roentgenogram with a wax pencil. When the lesions were too patchy or irregular to depict in this manner, color photographs were taken for future reference. The extent of small lesions was further investigated by additional transverse slices in the original segment. All evident and suspicious gross lesions were checked by microscopic blocks, which were taken so as to include the entire thickness of the ventricular wall. In the absence of gross lesions, the number and location of microscopic blocks depended upon the clinical and electrocardiographic findings. When a lesion was suspected from the electrocardiogram, the injection studies, or the gross appearance, but could not be positively identified or delineated by gross examination, it was customary to take a series of blocks around the entire circumference of the ventricle at one or more levels. The location of all microscopic sections was marked on the roentgenogram with wax pencil. Sections were read at a later date without knowledge of clinical or gross findings. Whenever there was a discrepancy between the electrocardiographic, gross, and microscopic findings, the gross specimen was re-examined and additional sections taken. If the microscopic sections failed to confirm the gross diagnosis, the outlines of the lesion as drawn on the roentgenogram were corrected so as to correspond with the microscopic findings. All major coronary arteries were opened by multiple transverse sections to check roentgenographic findings as to patency or obstruction, and to estimate degree of sclerosis. The relative size of the right and left ventricles was estimated in two different ways: (1) Measurements of the thickness of the roentgen image of the right and left ventricular walls were made at a number of points and the range and average thickness of each ventricle determined. (2) The ventricular segments were separated through an incision made at their juncture in the interventricular septum according to the technique of Stofer and Hiratzka,²⁰ and a

ratio was calculated, using the combined weights of the left ventricular segments as the numerator and the combined weights of the right ventricular segments as the denominator.

Material.—In this communication, an analysis is presented of the precordial electrocardiograms of the cases whose hearts were considered normal at autopsy on the basis of the following criteria: total weight below 400 grams in the male and below 350 grams in the female; ventricular ratio in the normal range of 1.6 to 2.0; normal myocardium to gross and microscopic examination.

A total of fifty-two cases satisfied the foregoing criteria and forms the basis of this study. The youngest patient was 19 years of age and the eldest was 87. The distribution by decade was as follows: second, one case; third, four cases; fourth, eight; fifth, eight; sixth, thirteen; seventh, fourteen; eighth, three; and ninth, one case. The series comprised thirty-six men and sixteen women. Death was due to noncardiac causes in all cases, the major factors being malignancy in nineteen, cirrhosis in nine, terminal pneumonia in seven, tuberculosis in four, postoperative in four, and miscellaneous conditions in the remainder. The precordial electrocardiogram consisted of Leads V_1 through V_6 inclusive in twenty-five cases and of Leads V_2 , V_4 , and V_6 in the remainder.

By means of a Cambridge measuring device,* the following intervals were determined in Leads V_1 , V_2 , V_5 , V_6 , aV_R , and aV_L : time from onset of QRS to (1) nadir of Q, (2) peak of R, (3) nadir of S, and (4) end of QRS. At least three representative complexes were measured in each lead and the average value was taken. Electrocardiograms were discarded as unsuitable for measurement when the response to the standardizing current consumed more than 0.02 second or when overshooting was present. Although the measurements were made to the nearest thousandth of a second, the error reached ± 0.005 second in some cases due to difficulty in determination of the precise onset or end of the QRS. Measurements by the Cambridge device are too time consuming for general usage and estimations with the aid of a hand lens are sufficiently accurate for routine electrocardiographic interpretation.

The average amplitude of each phase of the QRS was also determined, measurements being made from the top of the isoelectric line to the peak of an upright deflection and from the bottom of the isoelectric line to the nadir of a downward deflection. Correction was made for errors of standardization. The position of the RS-T junction in reference to the isoelectric line, the contour of the RST segment, and the direction and amplitude of the T wave were also recorded.

RESULTS

P wave was invariably upright in Leads V_4 , V_5 , and V_6 . It was usually less than 1.0 mm. in amplitude and did not exceed 2.0 millimeters. In Leads V_1 , V_2 , and V_3 an upright P wave was the most frequent finding, but a diphasic (\pm) deflection was present in V_1 in 32 per cent, in V_2 in 10 per cent, and in V_3 in 8

*We are greatly indebted to Dr. Frank N. Wilson for the loan of his Cambridge measuring instrument and for much helpful advice and criticism.

per cent of the cases. The diphasic P waves showed a steep intrinsicoid deflection, indicating proximity of the electrode to the right atrium. The amplitude of these diphasic P waves, measured from the isoelectric line to the peak of the positive or to the nadir of the negative phase, did not exceed 2 millimeters. An inverted P wave was encountered in V_1 in only one case.

Duration of QRS was determined in Leads V_2 and V_6 in all fifty-two cases and in Leads V_1 and V_5 in twenty-five of the group. The results are recorded in Table I. The measurement in Lead V_2 was, as a rule, slightly greater than in leads further removed from the heart, such as V_6 . Such a discrepancy would suggest that a portion of the tracing at the beginning or end of the QRS was isoelectric in the more remote precordial leads, due to decrement of potential with increasing distance from the heart. The QRS interval in Lead V_2 ranged from 0.064 second to 0.098 second, and averaged 0.078 second. It is noteworthy that the longest QRS interval in this series did not exceed 0.10 second in any of the leads measured. When QRS duration was compared with heart weight, a trend was found toward slightly longer QRS duration with increasing weight, but no close correlation could be made out. The longest QRS interval in any precordial lead averaged 0.077 second in the cases whose heart weight was below 250 grams, 0.079 second in those with cardiac weight between 250 and 300 grams, and 0.081 second in those in the 300 to 350 gram range.

Time of Onset of Intrinsicoid Deflection.—The time interval from the onset of the QRS to the peak of the R wave (that is, onset of intrinsicoid deflection) is a rough measure of the time elapsing from the arrival of the impulse in the ventricles to the completion of activation of the segment of wall beneath the exploring electrode. This interval was invariably shortest in Lead V_1 , progressively increased as the electrode was moved toward the left, and was longest in Lead V_6 in all but three cases, where it was maximal in V_5 . In these cases the voltage and total duration of the QRS was greater in Lead V_5 than in V_6 , suggesting that the string may have been isoelectric in Lead V_6 for a brief period at the beginning of ventricular activation. The difference in time of onset of the intrinsicoid deflection in leads over the right and left ventricles is significant, as shown by measurements ranging up to 0.023 second and averaging 0.014 second in Lead V_1 , and measurements ranging from 0.020 to 0.050 second and averaging 0.034 second in Lead V_6 . The measurements in a representative lead over the left ventricle exceeded those in a representative lead over the right ventricle by 0.03 second in one case, 0.025 to 0.03 second in five cases, 0.02 to 0.025 second in fourteen cases, 0.015 to 0.02 second in fifteen cases, 0.010 to 0.015 second in three cases, and by less than 0.010 second in two cases. Figures were not derived for eleven cases due to insufficient leads over the right ventricle. The maximal time interval from onset of QRS to peak of R could not be correlated with heart weight in the group of normal hearts, as shown by an average value of 0.035 second for those with heart weight below 250 grams, 0.033 second for those between 250 and 300 grams, and 0.036 second for the cases in the 300 to 350 gram range.

TABLE I. FINDINGS IN CHEST LEADS OF FIFTY-TWO PERSONS WHOSE HEARTS WERE NORMAL

LEAD	TOTAL NO. CASES	NO. WITH QS	NO. WITH Q	AMPLITUDE												DURATION																
				Q WAVE			R WAVE				S WAVE				R $\frac{R}{S}$ RATIO			TOTAL QRS			ONSET QRS TO NADIR OF Q			ONSET QRS TO PEAK OF R			ONSET R TO PEAK OF R			ONSET OF QRS TO NADIR OF S		
				MIN.	MAX.	AV.	NO.	MIN.	MAX.	AV.	NO.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.
V ₁	25	4	0	0	0	0	21	0	7	2.3	25	2.	24	10.5	0	0.4	4.5	.058	.092	.077	0	0	0	0	.023	.014	0	.023	.014	.017	.059	.040
V ₂	52	2	0	0	0	0	50	0	12	4.7	52	5.	38	13.4	0	0.50	2.76	.064	.098	.078	0	0	0	0	.036	.018	0	.036	.018	.025	.055	.045
V ₃	25	0	0	0	0	0	25	2	27	8.6	25	3.	21	8.8	7.	0.25	1.2															
V ₄	52	0	4	0	2	.076	52	2	25	13.0	52	0.5	14	5.4	1.42	0.02	0.41															
V ₅	25	0	10	0	1	0.24	25	3	21	10.7	17	0	10	1.7	0.75	0.16	0.16	.059	.089	.075	0	.016	.012	.014	.037	.026	.014	.037	.026	0	.075	.052
V ₆	52	0	33	0	2	0.49	52	3	19	9.2	17	0	3	0.42	0.4	0.05	0.05	.062	.098	.075	0	.022	.012	.020	.037	.027	.034	.037	.027	0	.076	.053

Duration of R Wave.—The time interval from onset of the R wave to its peak is representative of the time required for the impulse to pass through the segment of ventricular wall beneath the exploring electrode. This interval was invariably shortest in Lead V_1 , increased progressively in leads further to the left, and usually reached a maximum in Lead V_6 , occasionally in V_5 . The duration of the R wave in Lead V_1 ranged from 0 to 0.023 second, averaging 0.014 second; in Lead V_6 the range was from 0.020 to 0.037 second and the aver-

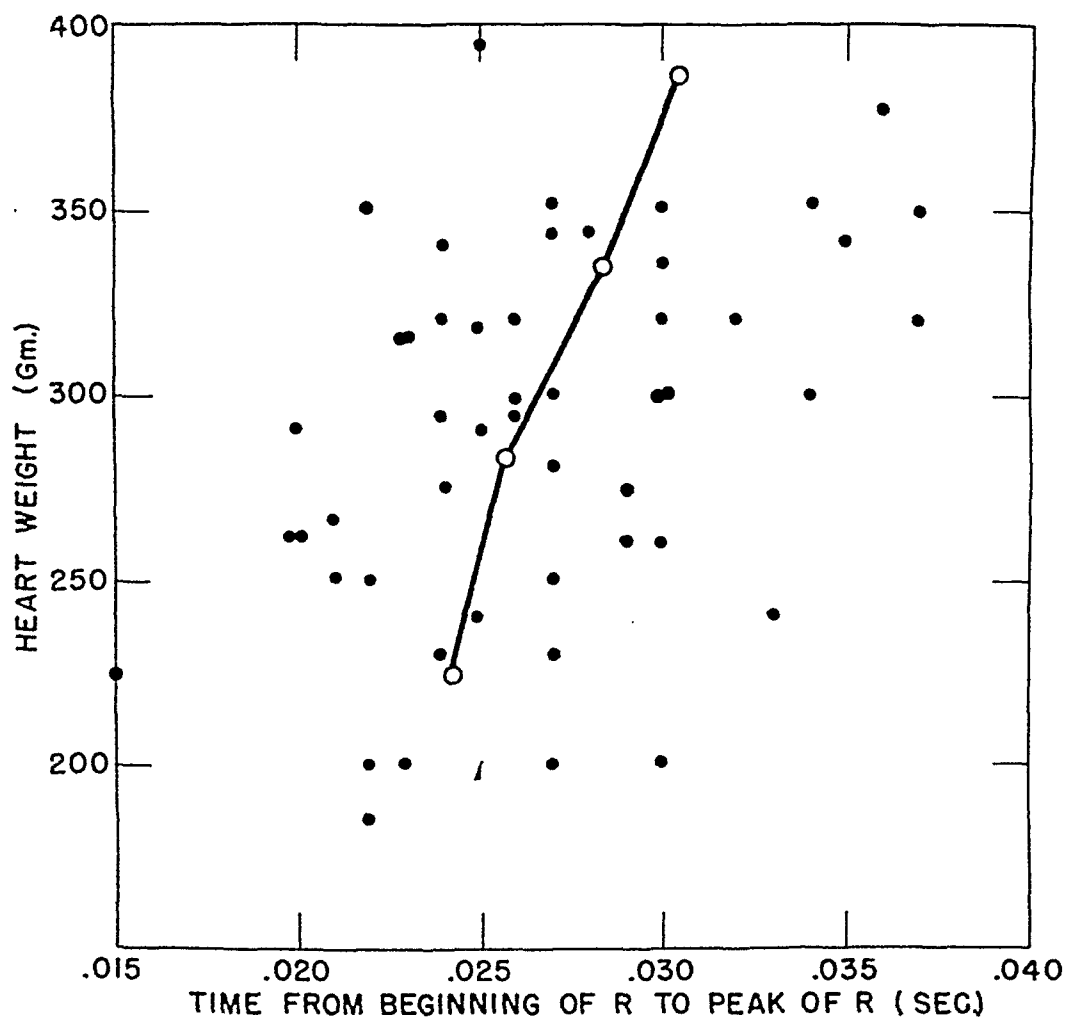


Chart I. Relation of duration of ascending limb of R wave in Leads V_5 or V_6 to heart weight.

age was 0.027 second. The measurement in a representative lead over the left ventricle exceeded that in a representative lead over the right ventricle by 0.02 to 0.025 second in four cases, 0.015 to 0.02 second in nine, 0.01 to 0.015 second in thirteen, and by less than 0.01 second in fifteen cases. When the time interval from onset to peak of R wave was plotted against heart weight, a trend was found toward a slightly longer duration of the R wave with increasing cardiac weight (Chart I). The maximal duration of the R averaged 0.024 second in the cases of patients with cardiac weight below 250 grams, 0.026 second in those between 250 and 300 grams, and 0.028 second in those in the 300 to 350 gram range.

Duration of Initial Deflection of QRS.—In Lead V_1 a small initial R, followed by a deep S, was found in twenty-one cases, and a QS deflection was the sole representative of the complex in the other four tracings. The initial deflection in Lead V_2 was upright in fifty cases. In the two remaining cases, a QS complex in V_2 accompanied a similar deflection in Lead V_1 , as illustrated by Fig. 1, *B*. The initial deflection in Lead V_3 was upright in all twenty-five cases in this series. However, when V_3 exhibits a tall R wave of left ventricular origin, a very small initial Q wave may be found in this as well as in leads further to the left. The incidence of an initial Q wave was 7.7 per cent in Lead V_4 , 40 per cent in V_5 , and 63.4 per cent in Lead V_6 . Illustrations are given in Fig. 1, *C, D, F*, and *G* and Fig. 2, *B, E*, and *H*. The maximal voltage of the Q wave in these three leads was 0.2 millivolt. The amplitude of the Q wave was invariably less than 25 per cent of the amplitude of the succeeding R wave. The ratio of Q to R ranged from 3 per cent to 20 per cent in Lead V_6 and from 3 per cent to 12 per cent in Lead V_5 . The time interval from onset to nadir of the Q wave was short, as exemplified by the measurements in Lead V_6 , which ranged from 0.006 second to 0.022 second, and averaged 0.012 second.

Location of Transitional Zone and Zones of Reference of the Potential Variations of the Right and Left Ventricles.—If a sufficient series of precordial leads is taken to cover both ventricles, a sharp contrast should be demonstrable between tracings from the left axilla (that is, Lead V_6), which reflect the potential variations of the epicardial surface of the left ventricle, and tracings from the right side of the precordium (that is, Lead V_1), which reflect principally the potential variations of the right ventricle. A study of Fig. 1 reveals that the $\frac{R}{S}$ -ratio in

Lead V_6 differs strikingly from that in Lead V_1 in every tracing except those of Case F, which will be discussed separately later. Furthermore, a transition from the pattern in V_1 to that in V_6 is demonstrable in leads from intervening points in all tracings of Fig. 1 except those of Case F. Among the remaining twenty-four normal cases in which all six of the precordial leads were available, the R wave first exceeded the S wave in Lead V_3 in thirteen cases (for example, Fig. 1, *C* and *I*), in V_4 in nine cases (for example, Fig. 1, *G*), and in Lead V_5 in two cases (Fig. 1, *A* and *H*).

The transition is sometimes abrupt, as in Fig. 1, *G*, where Lead V_3 displays a small R and deep S and the adjoining Lead V_4 displays a tall R and small S. Since the QRS complex in Lead V_3 resembles that in leads further to the right, and the QRS in V_4 corresponds to that in leads further to the left, it would appear that the electrode lies over the right ventricle at Position V_3 and crosses the interventricular septum to lie over the left ventricle at Position V_4 . An abrupt transition between two successive precordial leads tends to occur when the septum is more or less perpendicular to the pathway of the electrode across the precordium. In other cases the transitional zone is marked by a slurred or notched complex of relatively low voltage, composed of an R and S deflection of approximately equal amplitude. Such complexes are intermediate in form between those of right and of left ventricular origin and are presumably ob-

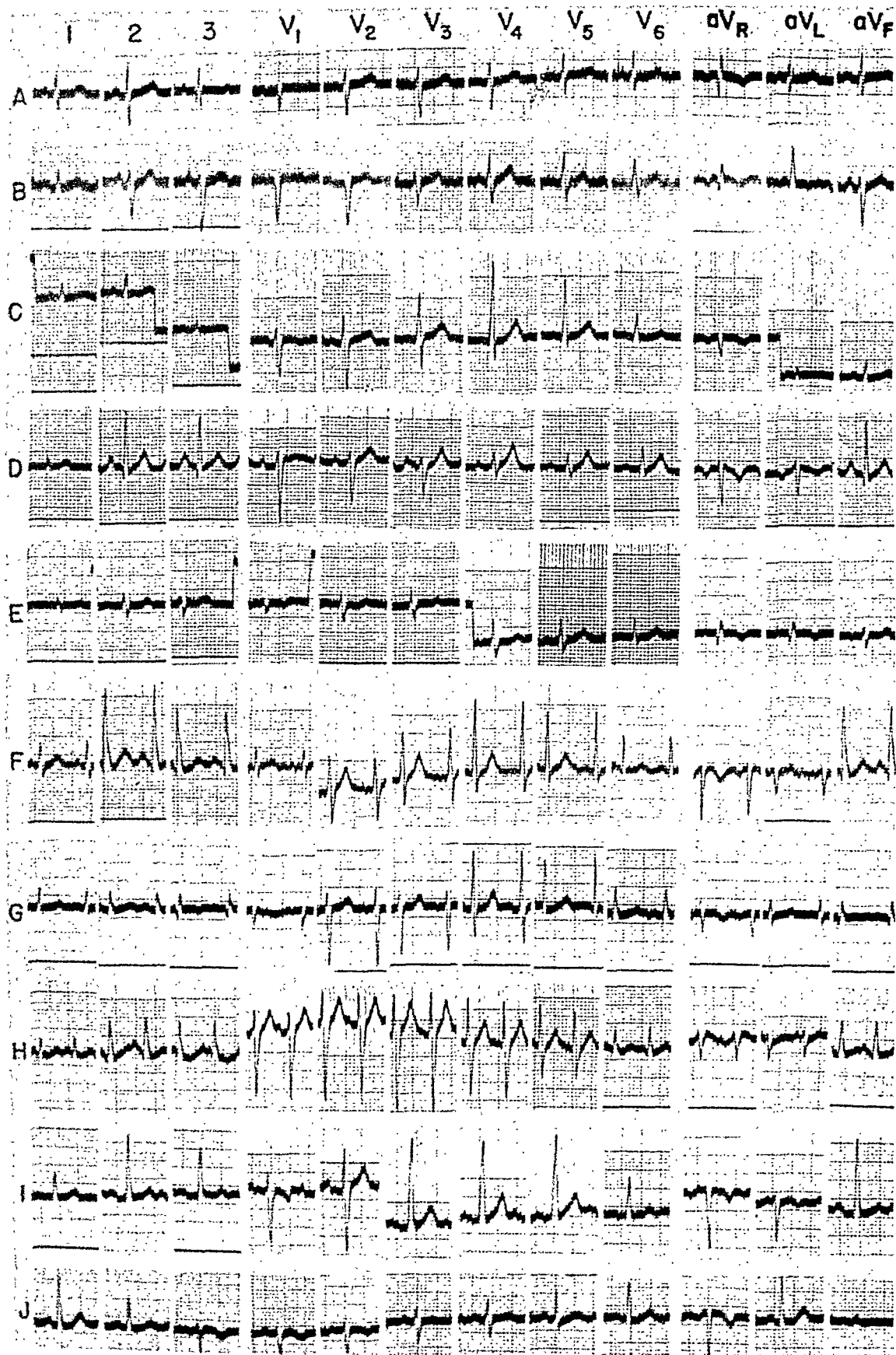


Fig. 1.—Normal variations in the precordial leads.

tained when the precordial electrode lies over the interventricular septum. A more gradual transition may occur when the apex is displaced backward, or the pathway of the electrode from Position V_2 to Position V_4 is parallel to the septum, as illustrated by Fig. 1, *A*, *D*, and *E*. The relatively low voltage and slurring of the QRS in Leads V_3 , V_4 , and V_5 of Fig. 1, *D* would suggest that the pathway of the electrode is nearly parallel to the septum.

Voltage of QRS.—The amplitude of both the R and S waves in every precordial lead is normally subject to wide variation, as is evident from study of Table I. The greatest range was found in Lead V_3 or V_4 , depending upon whether the electrode was at the transitional zone, to the right, or to the left. Although R waves of large amplitude tend to be associated with ventricular hypertrophy, voltages in the same range were found in several normal cases in this series. Low voltage R waves less than 0.7 millivolt in all six precordial leads were found in four normal subjects in this series, as illustrated by Fig. 1, *A*, *D*, and *E*.

Relative Amplitude of the R and S Waves in Each Precordial Lead.—The voltage of the R wave was invariably less in Lead V_1 than in any other lead. The R wave was absent from Lead V_1 in four of the twenty-five cases and was relatively small in the remainder, ranging from 1 mm. to 7 mm., and averaging 2.3 millimeters. As the electrode was moved toward the left, a progressive increase in the amplitude of the R was noted in every case to reach a maximum at Position V_3 in four cases, at V_4 in thirteen cases, at V_5 in six cases, and at Position V_6 in two cases. On the other hand, the S wave attained its maximal amplitude in leads over the right ventricle, sometimes at Position V_1 , as in the case shown in Fig. 1, *D*, but more often at Position V_2 , as shown in Fig. 1, *G*. As the electrode was moved from positions over the right to positions over the left ventricle, the S wave progressively diminished and was either absent from Lead V_6 or of minimal amplitude in this lead. The relationship of the R and S waves in each precordial lead is best expressed in terms of a ratio, calculated with the amplitude of R as a fixed figure in the numerator and the proportionate amplitude of S as a variable figure in the denominator. The ratio of R to S was always lowest in Lead V_1 and progressively increased as the electrode was moved to the left. This is illustrated by the average values for $\frac{R}{S}$ ratio, which were $\frac{1}{4.5}$

in Lead V_1 , $\frac{1}{2.8}$ in V_2 , $\frac{1}{1.2}$ in V_3 , $\frac{1}{0.41}$ in V_4 , $\frac{1}{0.16}$ in V_5 , and $\frac{1}{0.04}$ in Lead V_6 . These figures bring out the reciprocal relationships of the R and S waves in leads over the right and left ventricles.

Contour of QRS.—The QRS in the precordial leads is normally smooth in contour except when the complex is of low voltage or when the lead is at the transitional zone. Since the thickness of the string shadow is proportional to the distance traversed in a given period of time, the shadow cast by a QRS deflection of low voltage will be much thicker than that cast by a deflection of high voltage completed in the same period of time. This tends to convey the

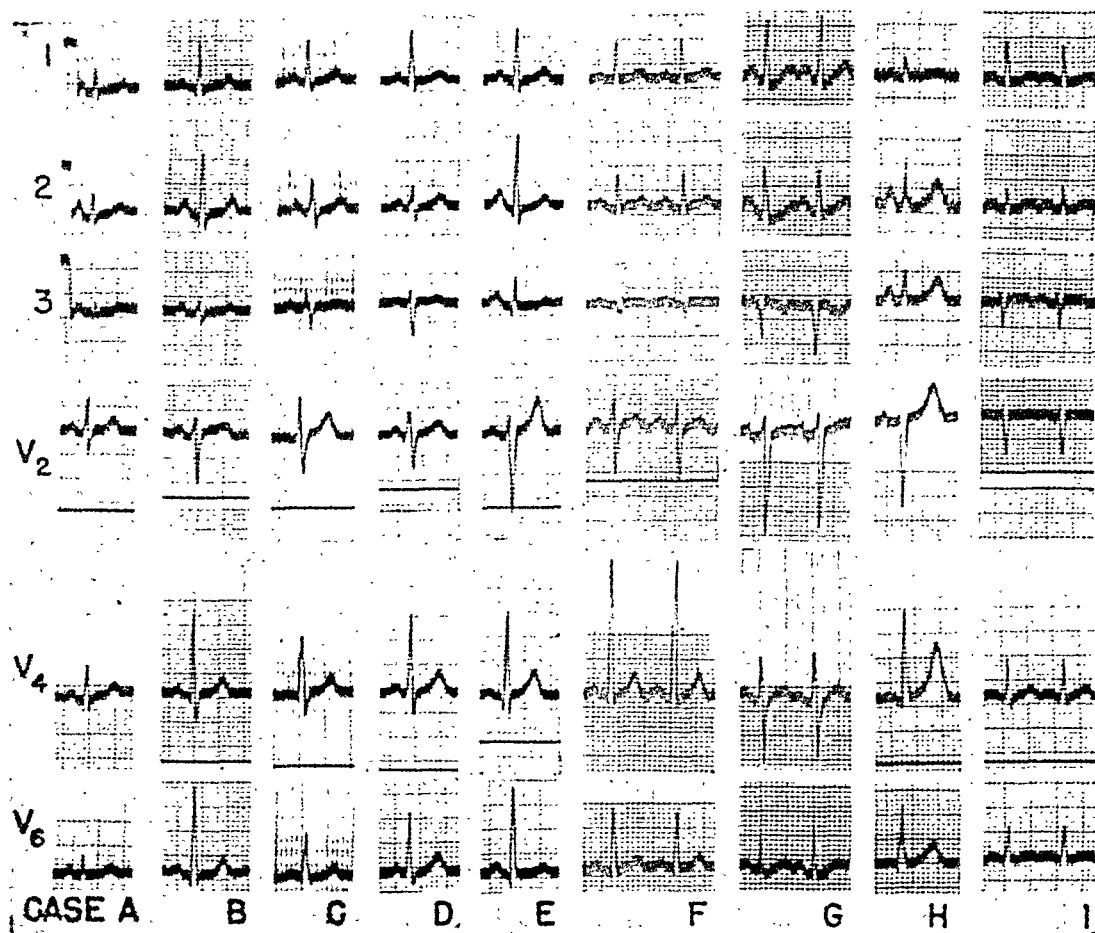


Fig. 2.—Normal variations in the precordial leads.

impression that a QRS of low voltage is slurred, as exemplified by Fig. 1, *E*. The fact that the duration of the QRS is within the normal limits of 0.10 second indicates that the relatively thick QRS tracing is secondary to the low voltage and not due to an intraventricular conduction defect. The QRS registered at the transitional zone, with the exploring electrode lying over the interventricular septum, may normally exhibit notching or slurring (as in Lead V_2 of Fig. 2, *B* and *D*, and in Leads V_3 and V_4 of Fig. 1, *D*), probably due to a greater admixture of potential variations from the two ventricles.

QT interval was below the upper limits of normal, as determined from the table of Ashman and Hull,²¹ in all but two cases where borderline values were obtained.

RS-T junction was determined in portions of Leads V_1 , V_2 , V_5 , and V_6 , where the T-P interval following a cycle was on the same horizontal level as the T-P interval preceding the cycle. The incidence of an isoelectric RS-T junction was as follows: in Lead V_1 , 88 per cent; in V_2 , 69 per cent; in V_5 , 88 per cent; and in Lead V_6 , 92 per cent. An elevation of 0.5 to 1.5 mm. was found three times in Lead V_1 , thirteen times in V_2 , once in V_5 , and twice in Lead V_6 . An elevation of 2 mm. was present in Lead V_2 of one case, this constituting the

sole instance of displacement exceeding 1.5 millimeters. In all cases with RS-T elevation, the RS-T segment and T wave were normal in shape. An RS-T depression of 0.5 to 1.0 mm. appeared to be present in one or more precordial leads of six cases. The apparent RS-T depression in each case could be ascribed to one of the following factors: (1) a prominent auricular T wave, as in Leads V_4 and V_6 of Fig. 2, *B*, which should be suspected when the P wave is tall and is recognized from the presence of a corresponding depression in the interval between the end of the P and the onset of the QRS; (2) the presence of a tachycardia sufficient to cause superimposition of the P wave on the antecedent T and thereby prevent the usual diastolic return of the string to the isoelectric line, as in Fig. 2, *F* and *I*. When a large auricular T wave coexists with tachycardia, a very pronounced pseudodepression of the RS-T junction may occur, as exemplified by Fig. 2, *G*. The apparent depression of the RS-T junction in Leads V_4 and V_6 of this case may be explained partly by the fact that the P wave begins before the T is completed and partly by the presence of a large auricular T wave, which may be seen between the end of the P and the onset of the QRS. This interpretation was borne out by the negative autopsy findings in this patient.

Contour of RS-T Segment.—The tracing may immediately slope away from the RS-T junction to form the T wave, or it may pursue a horizontal course for a variable period, ranging from 0.02 to 0.16 second. The RS-T segment, in the strict sense of the term, refers to the portion of the tracing between the RS-T junction and the point where the string slopes away from the horizontal. It is often difficult or impossible to demarcate the end of the RS-T segment from the beginning of the T wave and it is unnecessary to do so, since the duration of the RS-T segment is of little clinical significance. More important is the general shape of the tracing between the RS-T junction and the summit of the T wave. The contour of this portion of the tracing is normally related to the direction of the T wave. In the seven cases with inverted T wave in Lead V_1 and in the three cases with inverted T wave in Lead V_2 , the portion of the tracing between the RS-T junction and nadir of the T wave described a curve with upwardly directed convexity. In 92 per cent of the leads with upright T, this segment described a curve with upwardly directed concavity and in the remainder, this segment sloped straight upward to the summit of the T. Loss of the customary curvature was associated with tachycardia and was not due to digitalis in any case.

T wave was subject to considerable variation in Lead V_1 . It was upright in sixteen cases, isoelectric in two, and inverted in seven. The deepest negative T wave in this lead was 2 mm. in amplitude. The T wave in Lead V_2 was upright in forty-nine cases and exceeded an amplitude of 5 mm. in six of these. Three women, aged 19, 31, and 45 years, had inverted T waves in V_2 , measuring 1.0, 2.0, and 1.0 mm., respectively (Fig. 1, *J*). It was noteworthy that two nodal premature beats occurring in Lead V_2 of the 31-year-old woman showed a comparable QRS, but an erect T wave. The T wave was upright in Leads V_3 , V_4 , V_5 , and V_6 , except in two cases. One of these had an isoelectric T wave in

Lead V_3 , occurring as a transitional phenomenon between an inverted T_2 and upright T_4 (Fig. 1, J); the other had an isoelectric T wave in Lead V_6 associated with low voltage of the QRS, but a low upright T wave in Lead V_5 . The T wave was characteristically smooth in contour in precordial leads, but may be slightly notched in the leads at the transitional zone. The U wave was usually visible when the heart rate was below 100 per minute and was upright in direction.

DISCUSSION

Factors Governing the Form of the QRS in Direct Leads and in Precordial Leads.—Since the findings obtained by multiple direct leads from the epicardium of animals constitute the basis for the utilization and interpretation of multiple precordial leads in humans, a brief résumé of present concepts as to the mechanism of ventricular activation in relation to formation of the QRS will be given as an introduction to the discussion of our studies. The following summary is based principally on the work of Wilson and associates.²⁻⁵

The ventricular wall is normally set into activation by impulses distributed through the Purkinje network. After arrival at the subendocardial layer, the impulse passes centrifugally toward the epicardium at a rate of approximately 400 mm. per second, and successively activates each responsive muscle cell in its pathway. As the impulse reaches a given cell, it produces a sudden decrease in the impedance of the cell membrane, accompanied by an abrupt drop in electromotive force across this membrane. The cell undergoing excitation becomes negative in respect to the resting cells superficial to it and current flows from points just ahead of the impulse into the cell just behind it. The negative potential of the cell undergoing activation is transmitted backward through the intervening deeper layer of myocardium into the ventricular cavity and the positive potential of the resting muscle ahead of the advancing impulse is transmitted to the epicardium and chest wall.

An exploring electrode attached to the epicardium and connected with a sensitive galvanometer will register a positive potential as soon as the impulse reaches and starts to activate the subendocardial muscle directly beneath. With the galvanometric connections now in use, this results in an R wave, which continues upward until the arrival of the impulse at the epicardial surface, at which time the potential of the exploring electrode suddenly falls, as manifest by a precipitous downstroke called the intrinsic deflection. Therefore, the ascending limb of the R wave of direct leads is primarily a record of positive potential referred to the epicardial surface from electromotive forces created by the activation of the underlying wall, whereas the precipitous descending limb reflects the abrupt disappearance of these forces after arrival of the impulse at the epicardial surface. The time interval from onset to peak of the R wave and the amplitude of the R wave vary with the thickness of the ventricular wall beneath the exploring electrode, and are significantly less in direct leads from the relatively thin normal right ventricle than in direct leads from the relatively thick normal left ventricle.

Impulses distributed through the Purkinje system start to penetrate the interventricular septum and adjacent anterior wall of the ventricles a short time prior to their arrival at the lateral and posterior walls of the left ventricle. During this brief interval, negative potentials referred to the cavity from activation of septum and anterior wall will be transmitted through the as yet unactivated lateral and posterior walls, to be recorded through an overlying exploring electrode as an initial downward deflection, or Q wave. As soon as the impulse reaches and starts to activate the muscle directly beneath the electrode on the lateral or posterior wall, an abrupt reversal in the polarity of the exploring electrode will occur and the Q wave will be replaced by an R. If activation is still in progress in some more remote portion of the ventricle after its completion in the region to which the exploring electrode is attached, the negative cavity potentials will be transmitted through the completely depolarized wall to the surface, causing the intrinsic movement to continue downward below the isoelectric line as an S wave. Hence, the Q wave will be absent in records from portions of the wall that are first to become activated (the anterior wall of both ventricles adjacent to the septum) and normally will be deepest and broadest in records from portions which are last to become activated (lateral and posterobasal wall of left ventricle). On the other hand, the S wave will be deepest in tracings from portions of the wall where activation is completed first (normally in leads from the right ventricle) and will be absent in tracings from portions of the wall where activation is completed last (lateral and posterobasal walls of left ventricle).

The QRS pattern recorded through a direct epicardial lead will, therefore, depend upon the amount of responsive muscle in the subjacent ventricular wall and the time of onset and completion of its activation in reference to other portions of the ventricles. With defective conduction in one ventricle, the time interval from onset to peak of R is lengthened in leads over that ventricle, whereas the S wave is exaggerated in leads over the opposite ventricle. Abrupt changes in QRS are demonstrable when the electrode is moved from a normal to an infarcted segment of ventricle. If the entire wall is infarcted, only a QS complex is registered through overlying direct leads, the R wave being absent because of failure of development of electromotive force in the underlying wall. If only the subendocardial layer is destroyed, the Q wave is abnormally increased and the R diminished due to delayed onset of activation of the residual subepicardial muscle and reduced magnitude of the electromotive force. These examples are sufficient to bring out the advantage of multiple over single direct leads in the evaluation of a given ventricle and in the detection of localized lesions.

The potential variations of a precordial electrode are dominated by a much larger segment of ventricular wall than those of a direct lead because of the larger electrode employed for precordial than for direct leads and because of the greater distance from the heart. Nevertheless, comparison of tracings obtained by precordial leads with those obtained by direct leads from the subjacent epicardium ordinarily reveals a fairly close correspondence in general contour and in the relative duration and amplitude of the individual components

of the QRS complex. Tracings obtained by precordial leads are lower in voltage and show a less precipitous downstroke following the peak of the R. This downward movement is, therefore, more appropriately designated as an intrinsicoid deflection. The fairly close correspondence between direct and precordial leads obtains as long as the segment of ventricular wall beneath the exploring electrode is more or less uniform in thickness and in electrophysical activity, as in normal hearts, ventricular hypertrophy, bundle branch block, and so forth, but would not obtain in the presence of a very small myocardial lesion confined to only a portion of the area covered by the precordial electrode. Thus, with the foregoing limitations the demonstrated relationships of the QRS pattern of direct leads to the underlying myocardium in animals can be applied to the interpretation of multiple precordial leads in humans.

When the heart is in normal position, leads from precordial points V_1 and V_2 correspond roughly to direct leads from the epicardial surface of the right ventricle, whereas tracings made at Positions V_5 and V_6 correspond roughly to direct leads from the anterolateral surface of the left ventricle. The time interval elapsing from onset to peak of R wave in Leads V_1 and V_2 is an approximate measure of the time required for the passage of the impulse from the endocardial to epicardial surface of the anterior wall of the right ventricle, whereas the corresponding measurements in Leads V_5 and V_6 are an approximate index of the time required for activation of the anterolateral wall of the left ventricle. The relative amplitude of the R waves in Leads V_1 and V_2 on the one hand, and in Leads V_5 and V_6 on the other hand, serve as a rough index of the relative electromotive forces developed in the activation of the right and left ventricles, respectively. A minimum of two leads over each ventricle is desirable as a basis of comparison.

As the electrode is shifted from right ventricular position V_1 to left ventricular position V_5 , the normal electrocardiogram will show a progressive increase in the amplitude of the R wave and the time interval from the onset to the peak of the R, along with a progressive decrease in the amplitude of the S wave. This reflects the normal increase in thickness of ventricular wall as one moves from the anterior wall of the right ventricle to the lateral wall of the left. Small infarcts may result in abnormal increase in Q and reduction of R in a limited zone, amounting to little more than the diameter of the electrode. Thus, multiple precordial leads provide valuable information both for comparison of the two ventricles and for detection of localized lesions. The specific findings in this series of proven normal subjects remain for discussion.

Duration of QRS.—The average QRS interval of 0.078 second was identical with that found by McGinn and White²² in the standard leads of a group of one hundred normal adults. The upper limit of 0.098 second for the QRS interval is in accord with the findings of Wilson and Herrmann,²³ which were based on measurements of the standard leads of forty-nine autopsied cases. On the other hand, in virtually every large series in which the presence of a normal heart was established by physical and roentgen examination rather than by autopsy, a few cases have been encountered in which the QRS interval in the

standard leads amounted to 0.11 second or more.²⁴⁻²⁸ The higher range than in our series cannot be explained by the difference in leads selected, since measurements of QRS duration in precordial leads equal or slightly exceed measurements in standard leads, except in the presence of a localized conduction defect in the posterior ventricular wall. The fact that the QRS duration was confined within limits of 0.06 to 0.10 second in our series may be due merely to chance, operating in a relatively small group of cases. A larger series of electrocardiographic-autopsy correlations is needed to verify the occurrence and to determine the incidence of QRS intervals of 0.11 second or more in cases proven to have normal hearts by post-mortem examination.

Wilson and Herrmann²³ subdivided their cases according to ventricular weight and thickness of the left ventricle and noted that the mean QRS interval lengthened with increase in mean ventricular weight and thickness, but found a number of individual exceptions to these generalizations. They found an average QRS interval of 0.0649 second in cases with a ventricular weight below 150 grams, 0.0699 second for ventricular weights between 150 and 200 grams, and 0.0805 second for those exceeding 200 grams. It must be borne in mind that the figures represent weights of the ventricular segment only and that the group above 200 grams included cases of left ventricular hypertrophy. This probably accounts for the greater spread of values for QRS duration in the series of Wilson and Herrmann than in the cases reported in this communication. Comparison of individual cases in our series likewise revealed no consistent relation between QRS duration and ventricular weight. There was a trend toward slight lengthening of mean QRS duration with increase in mean cardiac weight, as shown by an average QRS interval of 0.077 second in hearts weighing less than 250 grams, 0.079 second in those between 250 and 300 grams, and 0.081 second in those weighing from 300 to 350 grams. These differences are not statistically significant.

Time of Onset of Intrinsicoid Deflection.—Kossmann and Johnston²⁹ obtained Leads V₁, V₂, V₃, V₄, and V₅ on thirty medical students with hearts which were normal to clinical and roentgen examination, and determined the time of onset of the intrinsicoid deflection with reference to the beginning of the QRS in the simultaneously taken standard Lead I. Our measurements, which were made from the beginning of the QRS to the onset of the intrinsicoid deflection in Leads V₁, V₂, V₅, and V₆, corresponded closely with their findings. For example, the interval preceding the intrinsicoid deflection in Lead V₁ averaged 0.017 second in their cases and 0.014 second in our series. Corresponding measurements in Lead V₂ were 0.019 second and 0.018 second. Their average in V₅ of 0.034 second was greater than our value of 0.030 second in this lead, but was similar to our finding of 0.034 second in Lead V₆. Their longest measurement was 0.055 second and was obtained in Lead V₄, whereas ours was 0.051 second and was found in Lead V₅. The maximal time interval from onset of QRS to peak of R could not be correlated with heart weight in our cases. Their observation that the time of onset of the intrinsicoid deflection was invariably later in leads from the left than in leads from the right side of the precordium

was confirmed in this study. The difference averaged 0.0194 second in their cases and 0.0192 second in our twenty-five cases in which measurements were available in Leads V_1 , V_5 , and V_6 . The greatest difference in measurements was found to be 0.030 second in both series and the smallest was 0.008 second in their series and 0.003 second in ours. Since the onset of the intrinsicoid deflection marks the arrival of the impulse at the epicardial surface beneath the exploring electrode, the longer intervals in leads over the left than in leads over the right ventricle would be expected in view of the normally greater thickness of the left ventricular wall.

The anticipated correlation between the time of onset of the latest intrinsicoid deflection and cardiac weight was not borne out in this study; however, when the time interval from the onset of the R to the peak of the R in Leads V_6 or V_5 was plotted against heart weight, a trend was found toward a slightly longer duration of the R wave with increasing cardiac weight. Since the interval elapsing from onset of R to its peak is an index of the time required for the impulse to pass from the endocardial to the epicardial surface of the segment of wall beneath the electrode, it is not surprising to find that this measurement is better correlated with cardiac weight than the time interval from the beginning of the QRS to the start of the intrinsicoid deflection. It is noteworthy that the longest measurement from the beginning to the peak of R in this series of normal hearts was 0.037 second, and that the value was below 0.035 second in all but five of the cases. The duration of the R wave was invariably greater in leads over the left than in leads over the right ventricle, the average difference being 0.013 second.

Direction of Initial Deflection of QRS.—The variable findings in Lead V_1 among normal subjects may be in part attributable to differences in the relation of the electrode to the underlying cardiac chambers. The electrode at Position V_1 may lie over the anterolateral wall of the right ventricle, in which event an initial R wave derived from activation of the subjacent right ventricular wall would be expected. In some cases, however, the electrode in Lead V_1 lies over the right atrium, and thus faces toward the atrioventricular orifices and is dominated by the potential variations of the ventricular cavities. Under such circumstances, the QRS may consist solely of a QS complex or may show a small initial R from momentary positivity of the right ventricular cavity. This may be due either to a slightly earlier onset of activation of the left than of the right half of the septum,³⁰ or to greater magnitude of electrical forces developed in the left than in the right side of the septum. This probably explains why an RS complex is a much more common normal finding in Lead V_1 than a QS complex. It should be emphasized that an initial Q followed by an RS does not occur as a normal finding in Leads V_1 or V_2 .

A QS complex may be found in both Leads V_1 and V_2 when the heart is displaced backward and to the left, thereby bringing the electrode into closer proximity to the right atrium. Evidence of such displacement in Case B of Fig. 1 is afforded by the shift in transitional zone to the left and by the prominent late R wave in Lead aV_R .²¹ Before considering the QS in both Leads V_1 and

V_2 as a rare normal variant, it is advisable to take additional leads from the right anterior chest. If the QS complexes in Leads V_1 and V_2 are due to displacement of the heart backward and to the left, a similar deflection should be obtained in Lead V_{3R} and in other leads from the right anterior chest wall. On the other hand, if the QS complex in Leads V_1 and V_2 is a remnant of an old anteroseptal infarction, a small initial R wave should be demonstrable in Lead V_{3R} or in Lead V_E . The Q wave which may be found normally in leads from the left axilla is merely an expression of the slightly later onset of activation of the lateral wall of the left ventricle than the septum and adjoining anterior wall. The normal Q in Leads V_4 , V_5 , and V_6 is brief in duration and small in amplitude. The time interval from onset to nadir should fall within a range of 0.005 to 0.02 second and the amplitude should be less than 25 per cent of that of the R wave in the same lead. When the time interval from onset to nadir exceeds 0.02 second and the amplitude exceeds 25 per cent of that of the R wave in the same lead, the Q wave is probably abnormal and most likely the result of infarct or fibrosis of the subendocardial portion of the underlying wall.

Location of transitional zone and zones of reference of right and left ventricular potentials is subject to considerable variation, even when the heart is normal in size. Individual variations are traceable to differences in the shape of the chest and in the position of the heart. In this study, as in that of Kossmann and Johnston,²⁹ the transitional zone was most commonly found between Positions V_2 and V_4 , leads to the right being dominated by potential variations of the epicardial surface of the right ventricle and leads to the left, by potential variations of the epicardial surface of the left ventricle. The QRS recorded at the transitional zone may normally exhibit notching or slurring,^{29,32} probably due to greater admixture of potential variations from the two ventricles. Kossmann and Johnston²⁹ found that a notch on the descending limb of the R wave was practically synchronous with the onset of the intrinsicoid deflections in leads further to the left, whereas a notch on the ascending limb of the R wave was practically simultaneous with the onset of the intrinsicoid deflection in leads further to the right.

Whenever the transitional zone is located somewhere between Positions V_2 and V_5 , a minimum of two out of the six precordial leads will be dominated by the potential variations of each ventricle, which generally makes the precordial electrocardiogram adequate for interpretation. In rare instances the transitional zone may be displaced to the right of Position V_2 or to the left of Position V_5 . This may cause confusion unless additional leads are taken further to the right and left, as illustrated by the patient whose tracing is shown in Fig. 1, *F*. In Leads V_1 and V_2 the R wave is relatively large in proportion to the S, a finding which would suggest right ventricular hypertrophy if the transitional zone were located in its usual position. However, the fact that the $\frac{R}{S}$ ratio in Leads V_1 and V_2 is comparable to that in leads further to the left would suggest that Leads V_1 and V_2 , like V_3 , V_4 , V_5 , and V_6 , reflect chiefly the potential variations of the left ventricle. The upright T wave of normal contour in V_1 and V_2 constitutes

further evidence against the presence of right ventricular hypertrophy. The patient whose tracings are shown in Fig. 1, *F* died before additional leads could be obtained, but autopsy revealed a normal right ventricle, thereby excluding right ventricular hypertrophy as a cause of the pattern in Leads V_1 and V_2 and lending indirect support to the supposition that the transitional zone was displaced to the right of the sternum. The foregoing case was discussed in some detail to emphasize the importance of obtaining additional precordial leads further to the right and left when the tracings obtained at the six customary points are more or less constant in form.

Voltage of QRS.—The average amplitude of the R wave in precordial Leads V_1 , V_2 , V_3 , V_4 , and V_5 of this series was approximately half that found by Kossmann and Johnston²⁹ in corresponding leads, in spite of the fact that the time interval during which the R wave was registered was almost identical in the two series. These differences are attributable, at least in part, to extrinsic causes. A greater loss of potential through the chest wall would be expected in our cases, since 60 per cent were in the age group over fifty years, in which emphysema is common, and 30 per cent were women, whose soft tissues are generally thicker than those of men due to the presence of the breasts.

Determination of the maximal amplitude of the R wave in the six precordial leads is of limited diagnostic value. Although R waves of large amplitude tend to be associated with ventricular hypertrophy, voltages in the same range may be obtained in some normal individuals, especially in young persons with thin chest walls. However, high voltage of the R wave, when accompanied by lengthening of the time interval between its onset and peak to 0.04 second or more, is highly significant and will be discussed in greater detail in a future communication.

R waves of low voltage (less than 0.7 mv. in all six precordial leads) should arouse suspicion of a myocardial lesion,³³ but were found in four normal subjects in this series. The only case in which the R wave was less than 0.5 mv. in all precordial leads had marked edema of the chest wall from superior vena caval obstruction produced by a mediastinal lymphosarcoma. The low voltage in one case (Fig. 1, *D*) could be attributed to vertical position of the heart, the forces derived from left ventricular activation being directed more downward than anteriorly, producing a tall R wave in Leads aV_F , II, III. The low voltage of the R in the two remaining cases (Fig. 1, *A* and *E*) could be ascribed to backward displacement of the apex, a greater portion of the forces derived from left ventricular activation being directed backward, causing a late R wave in Lead aV_R and a late S wave (and consequent reciprocal reduction in the R wave) in Leads V_4 , V_5 , and V_6 .

Relative Amplitude of R and S Deflections in Each Precordial Lead.—As the electrode was moved from Positions V_1 or V_2 toward the left, a progressive increase in the R wave and reciprocal decrease in the S wave was found in every case, thereby confirming the observations of Kossmann and Johnston.²⁹ The location of the maximal R was most commonly in Lead V_4 , but varied from V_3 to V_6 , depending upon the configuration of the thorax and position of the heart.

When the electrode was moved from Position V_4 to V_5 and then to V_6 , the most common finding was a progressive decrease in amplitude of the R wave due to increasing distance between the electrode and the left ventricle. The reverse relationship (that is, increasing amplitude of R wave) may occur as a normal variant when the heart is in vertical position and when the apex is displaced backward or to the left.

The S wave attained its maximal amplitude in leads over the right ventricle, sometimes in V_1 , but more often in V_2 . The S wave recorded in these leads was derived from activation of the outer wall of the left ventricle. As soon as the septum and right ventricular wall have become completely depolarized, the negative potentials referred to the left ventricular cavity from the continuing activation of the outer wall of the left ventricle are transmitted to electrodes overlying the right ventricle, to be registered as an S wave in these leads. There are at least two factors governing the relative amplitudes of the S waves in Leads V_1 and V_2 . The fact that the peak of the R wave is attained slightly earlier in V_1 than in V_2 allows a slightly longer interval for transmission of negative left ventricular cavity potentials to the electrode at Position V_1 than to that at V_2 , and thus tends to make the S wave deeper at Position V_1 . The greater distance from the left ventricular cavity to Position V_1 tends to cause a greater decrement in potential, and thus tends to make the S wave at V_1 smaller than that at V_2 . The resultant finding depends upon the balance between these two factors.

RS-T Segment.—An elevation in the RS-T junction of 0.5 to 1.5 mm. above the isoelectric line was a fairly common finding in this series, and an elevation of 2.0 mm. was present in one case. In view of the fact that normal elevation of the RS-T junction is associated with an abruptly rising RS-T segment and tall upright T wave, it is probable that the electromotive forces developed during repolarization have reached sufficient magnitude by the end of the QRS to account for the upward displacement of the RS-T junction. An elevation of the RS-T junction may be considered within normal limits if the displacement does not exceed 2.0 mm., and provided that the RS-T segment immediately begins to rise above the junction in an arc with upward concavity to end in a tall upright T wave. Depression of the RS-T junction is very rare in the precordial leads of normal electrocardiograms and should be regarded as abnormal if it amounts to 0.5 mm. or more, provided pseudodepression from tachycardia or an auricular T wave are excluded.

T Wave.—Suarez and Suarez, Jr.,³⁴ took electrocardiograms on thirty-one normal women between the ages of 19 and 45 years, and found inversion of the T wave in Lead V_2 in four cases and in Lead V_3 , as well, in one case. They attributed the inverted T waves to the persistence of the juvenile pattern into adult life. In a study of the CF leads on young adults with clinically normal hearts, Littmann³⁵ found that inversion of the T wave in Leads CF_2 , CF_3 , and CF_4 was more common among colored than white subjects and more frequent in women than in men. The T wave in Lead V_2 was upright in forty-nine of our cases and was inverted in one white girl, 19 years of age, and in two Negro women, 31 and 45 years of age. The T wave in Lead V_3 was isoelectric in the latter patient, but

was upright in the remaining fifty-one. Since the hearts were normal at autopsy and no cause for the T wave inversion was demonstrable, it was regarded as a normal variant, perhaps due to the persistence of the juvenile pattern. Inversion of the T wave in Leads V_4 , V_5 , and V_6 was not found in this series or in normal adults studied by Suarez and Suarez, Jr., and by Kossmann and Johnston. Flattening of the T wave in Lead V_6 is probably within normal limits when the QRS in this lead is low in voltage, but normal in configuration.

SUMMARY

1. Wilson precordial leads have been correlated with autopsy findings in a group of 1,000 cases. In this communication, an analysis is presented of the precordial electrocardiograms of fifty-two patients whose hearts were considered normal by gross and microscopic examination.

2. The P wave was consistently upright in Leads V_4 , V_5 , and V_6 and varied from erect to diphasic in Leads V_1 , V_2 , and V_3 , depending upon the position of the electrode in reference to the right atrium.

3. The total QRS interval and the duration of each component phase were determined in Leads V_1 , V_2 , V_5 , and V_6 with aid of a Cambridge measuring device. The average QRS interval was 0.078 second and the upper limit in this series was 0.098 second. There was a trend toward slight lengthening of QRS duration with increasing cardiac weight.

4. A QRS complex was found in both Leads V_1 and V_2 in two cases, but was not present in leads further to the left. An initial Q with succeeding R was not found in leads over the right ventricle, but was present in at least one lead over the left ventricle in approximately two-thirds of the cases. This Q wave was brief in duration, reaching its nadir within 0.02 second, and was small in magnitude, amounting to less than 25 per cent of the amplitude of the succeeding R wave.

5. The interval elapsing from the onset of the R wave to its peak was taken as an index of the time required for the impulse to pass through the segment of ventricular wall beneath the exploring electrode. The time interval from onset to peak of R was invariably minimal in Lead V_1 and increased progressively in leads further to the left to reach a maximum in Leads V_5 or V_6 . The significantly longer duration of the R wave in leads over the left than in leads over the right ventricle was in keeping with the normal difference in thickness of their respective walls. There was a trend toward a slightly greater duration of the R wave in Lead V_6 with increasing ventricular weight. As the electrode was moved from positions over the right to positions over the left ventricle, a progressive increase in the amplitude of the R wave and a reciprocal decrease in the S wave was found in every case. Low voltage R waves that were less than 7 mm. in height in all six precordial leads were found in four normal subjects in this series. Normal variations in the position of the transitional zone and form of QRS complexes recorded in this zone are illustrated and discussed.

6. An elevation of the RS-T take-off of 0.5 to 2.0 mm. may be considered as a normal variant, provided that the tracing immediately begins to rise above

the RS-T junction in an arc with upward concavity to end in a tall upright T wave. Depression of the RS-T junction is very rare in the precordial leads of subjects with normal hearts and should be regarded as abnormal if it amounts to 0.5 mm. or more, provided that pseudodepression from tachycardia or a prominent auricular T wave are excluded.

7. An inverted T wave was a frequent finding in Lead V_1 and was present in Lead V_2 in three normal women, 19, 31, and 45 years of age, respectively. The T wave was upright in Leads V_3 , V_4 , V_5 , and V_6 except in two subjects, one of whom had an isoelectric T in V_3 associated with an inverted T wave in Leads V_1 and V_2 . The other had an isoelectric T in Lead V_6 associated with low voltage of the QRS.

The electrocardiograms were taken and mounted by Miss Josephine McDonald and were retouched by Miss Evelyn Erickson and Miss Geraldine Chesney.

REFERENCES

1. MacLeod, A. G., Wilson, F. N., and Barker, P. S.: The Form of the Electrocardiogram. I. Intrinsicoid Electrocardiographic Deflections in Animals and Man, *Proc. Soc. Exper. Biol. & Med.* 27:586, 1930.
2. Wilson, F. N., MacLeod, A. G., and Barker, P. S.: Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7:305, 1932.
3. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: Interpretation of Galvanometric Curves Obtained When One Electrode Is Distant From Heart and Other Near or in Contact With Ventricular Surface; Observations on Mammalian Heart, *AM. HEART J.* 10:176, 1934.
4. Barker, P. S., MacLeod, A. G., and Alexander, J.: Excitatory Process Observed in Exposed Human Heart, *AM. HEART J.* 5:720, 1930.
5. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: Precordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
6. Wilson, F. N., Johnston, F. D., MacLeod, A. G., and Barker, P. S.: Electrocardiograms That Represent Potential Variations of Single Electrode, *AM. HEART J.* 9:447, 1934.
7. Eckey, P., and Fröhlich, R.: Zur Frage der Unipolaren Ableitung des Elektrokardiogramms, *Arch. f. Kreislaufforsch.* 2:349, 1938.
8. Burger, R.: Ueber die Herzferne Elektrode bei der semidirekten Ableitung; über die Nullpotentialelektrode von Wilson; über die Verwendung einer von der gesamten Körperoberfläche Ableitenden Elektrode als indifferente Test-Elektrode, *Cardiologia* 3:56, 1939.
9. Burger, R., and Wuhrmann, F.: Ueber das elektrische Feld des Herzens. 2. Mitteilung; Die Darstellung des elektrischen Feldes des Herzens durch das "Diagramm der Potentialdifferenzen." Der Vergleich dieses Diagramms mit dem Vektordiagramm, *Cardiologia* 3:139, 1939.
10. Wolferth, C. C., and Wood, F. C.: Prediction of Differences Between Precordial Leads CR, CL, and CF, Based on Limb Lead Findings, *AM. HEART J.* 20:12, 1940.
11. Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Distribution of Patterns of Ventricular Potential Which Determine Forms and Significance of Electrocardiograms, *Am. J. M. Sc.* 205:469, 1943.
12. Wosika, P. H.: Personal communication.
13. Goldberger, E.: Simple, Indifferent, Electrocardiographic Electrode of Zero Potential and Technique of Obtaining Augmented, Unipolar, Extremity Leads, *AM. HEART J.* 23:483, 1942.
14. Myers, G. B., and Oren, B. G.: Use of Augmented Unipolar Left Leg Lead in Differentiation of Normal From Abnormal Q-wave in Standard Lead III, *AM. HEART J.* 29:708, 1945.
15. Myers, G. B., Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, *AM. HEART J.* (In press).

16. Etheridge, C. B., and Stolar, M. H.: Simple Switching Device to Facilitate Recording of Electrocardiograms Embodying Multiple Types of Leads, *AM. HEART J.* 29:733, 1945.
17. Bryant, J. M., and Johnston, F. D.: Errors Encountered in the Use of the Goldberger Central Terminal, *J. Clin. Investigation* 25:919, 1946.
18. Schlesinger, M. J.: Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15:528, 1938.
19. Stofer, B. E.: Simplified Klotz-Maclachlan Solution for Temporary Color Preservation, *J. Lab. & Clin. Med.* 28:1629, 1943.
20. Stofer, B. E., and Hiratzka, T.: The Weight of Cardiac Ventricular Segments and Their Variations in Certain Diseases, (In preparation).
21. Ashman, R., and Hull, E.: Essentials of Electrocardiography for the Student and Practitioner of Medicine, Ed. 2, New York, 1941, The Macmillan Company, p. 344, Table III.
22. McGinn, S., and White, P. D.: The Duration of the QRS Complex in the Normal and Abnormal Electrocardiogram, *AM. HEART J.* 9:642, 1934.
23. Wilson, F. N., and Herrmann, G.: Relations of QRS-interval to Ventricular Weight, *Heart* 15:135, 1930.
24. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1000 Young Healthy Aviators, *AM. HEART J.* 27:524, 1944.
25. Stewart, C. B., and Manning, G. W.: Detailed Analysis of Electrocardiograms of 500 R. C. A. F. Aircrew, *AM. HEART J.* 27:502, 1944.
26. Lüderitz, B.: Ueber Beziehungen zwischen der Breite von QRS und der Form des ST-Stückes im menschlichen Ekg., *Arch. f. Kreislaufforsch.* 5:223, 1939.
27. Larsen, K., and Skulason, T.: The Normal Electrocardiogram, *AM. HEART J.* 22:625, 1941.
28. Viscidi, P. C., and Geiger, A. J.: Electrocardiographic Observations on 500 Unselected Young Adults at Work, *AM. HEART J.* 26:763, 1943.
29. Kossmann, C. E., and Johnston, F. D.: Precordial Electrocardiogram; Potential Variations of Precordium and the Extremities in Normal Subjects, *AM. HEART J.* 10:925, 1935.
30. Mahaim, I.: Nouvelles Recherches Sur Les Lesions Du Faisceau De His-Tawara, *Ann. de méd.* 32:347, 1932.
31. Goldberger, E.: Differentiation of Normal From Abnormal Q Waves, *AM. HEART J.* 30:341, 1945.
32. Roche, E.: Multiple Chest Lead Cardiograms and Their Clinical Value, *Brit. Heart J.* 7:119, 1945.
33. Bellet, S., and Kershbaum, A.: The Significance of Low Voltage of the QRS Complex in the Precordial Leads, *AM. HEART J.* 22:195, 1941.
34. Suarez, R. M., and Suarez, Jr., R. M.: The T Wave of the Precordial Electrocardiogram at Different Age Levels, *AM. HEART J.* 32:480, 1946.
35. Littmann, D.: Persistence of the Juvenile Pattern in the Precordial Lead of Healthy Adult Negroes, With Report of Electrocardiographic Survey on Three Hundred Negro and Two Hundred White Subjects, *AM. HEART J.* 32:370, 1946.

VARIATIONS IN THE FIRST HEART SOUND IN COMPLETE A-V BLOCK

OWEN W. BEARD, M.D., AND GEORGE M. DECHERD, JR., M.D.
GALVESTON, TEXAS

GRIFFITH¹ is generally credited with having first noted the marked variation in intensity of the first heart sound in patients with complete atrioventricular block, though Orias and Braun-Menendez² give credit for this observation to Straseschko. Griffith, using polygraphic records, concluded that intensification of the first sound resulted from ventricular contraction during auricular systole. The influence of varying time relationships between auricular and ventricular contractions upon the intensity of the first heart sound has been carefully studied by Wolferth and Margolies.³ They found that the first sound was most intense when the P wave preceded the QRS complex by 0.10 to 0.20 second, and that on both sides of this time interval there was diminution in the amplitude of the sound. This observation suggested to them that the position of the mitral valve leaflets at the beginning of ventricular contraction was an important factor in determining the loudness of the first sound. They felt that when the leaflets were wide open slight regurgitation might occur into the auricle, preventing a rapid rise in intraventricular tension; conversely, if the ventricular contraction occurred at a time when the leaflets were nearly closed, there might be a little or no interference with the rise in ventricular tension, thus leading, they thought, to a louder sound. Their deductions from application of the animal experiments of Dean⁴ led them to the conclusion that loud first sounds were produced when the mitral leaflets were nearly closed.

Dock⁵ has presented experimental evidence to support his belief that the first heart sound is entirely valvular in origin, and more recently⁶ has disputed the contradictory conclusions of Smith and associates.⁷

The present paper is substantially a repetition of the work done by Wolferth and Margolies; however, we used a different type of equipment, and have reached somewhat different conclusions. Six patients with complete A-V block, and with clinically normal A-V valves, have been studied. The heart sounds were recorded during expiration with the Electrocardiograph-Stethograph.* The amplitude in millimeters of the vibrations produced by the first heart sound was measured and graphed to show its time relationship to the preceding P wave of the simultaneously recorded electrocardiogram. Wiggers⁸ accepts the amplitude

From the Department of Medicine, University of Texas School of Medicine, and the Heart Station of the John Sealy Hospital, Galveston.

Received for publication Feb. 11, 1947.

*The Cambridge Instrument Co., Inc., New York. N. Y.

of the sound vibrations as a satisfactory index of their loudness. Sounds associated with a short R-P interval have been graphed twice; that is, also to show the long P-R interval of the preceding P wave.

The absolute amplitudes of the first heart sounds are comparable only in individual records, since the position of the microphone, the position of the patient, the tension of the elastic band holding the microphone, and the exact degree of amplification affect the height of the vibration in the sound record.

CASE REPORTS

CASE 1.—P. S., a student nurse, 19 years of age, was found to have complete atrioventricular dissociation when the members of her class were subjected to electrocardiographic study for another purpose. She had had no symptoms, though she had noted that her pulse rate had been about 50 per minute since February, 1945; she also had noted that her pulse rate increased slightly with exercise. She had had a severe sore throat at the age of 10 years and her left knee was painful and stiff for a period of two days two years later.

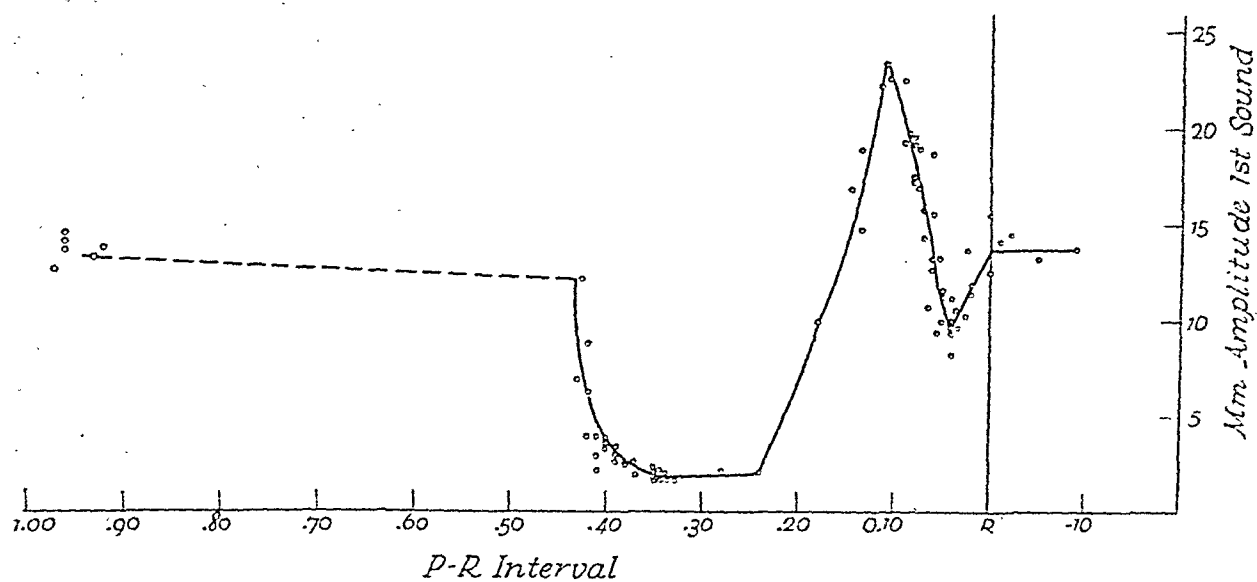
The blood pressure was 112/72. The cardiac rhythm was slightly irregular with marked variation in the intensity of the first heart sound. The pulmonary second sound was reduplicated. A very faint systolic murmur could be heard over all valve areas. The heart was normal in size to percussion and on fluoroscopic examination. The electrocardiogram showed complete atrioventricular block with supernormal conduction of some atrial impulses; intraventricular conduction was normal.

Fig. 1, *A*, shows the variations in amplitude of the first heart sound as related to the P-R interval. The atrial complexes with a P-R interval of about 0.35 to 0.43 second were those that were conducted to the ventricles. Injection of 1 mg. of prostigmine caused the disappearance of conducted beats, presumably by vagal depression of the conducting tissues; Fig. 1, *B*, illustrates the curve obtained after the injection of prostigmine. Injection of either atropine or epinephrine facilitated conduction so that there was 1:1 conduction, though the P-R interval was prolonged under these circumstances to 0.35 second.

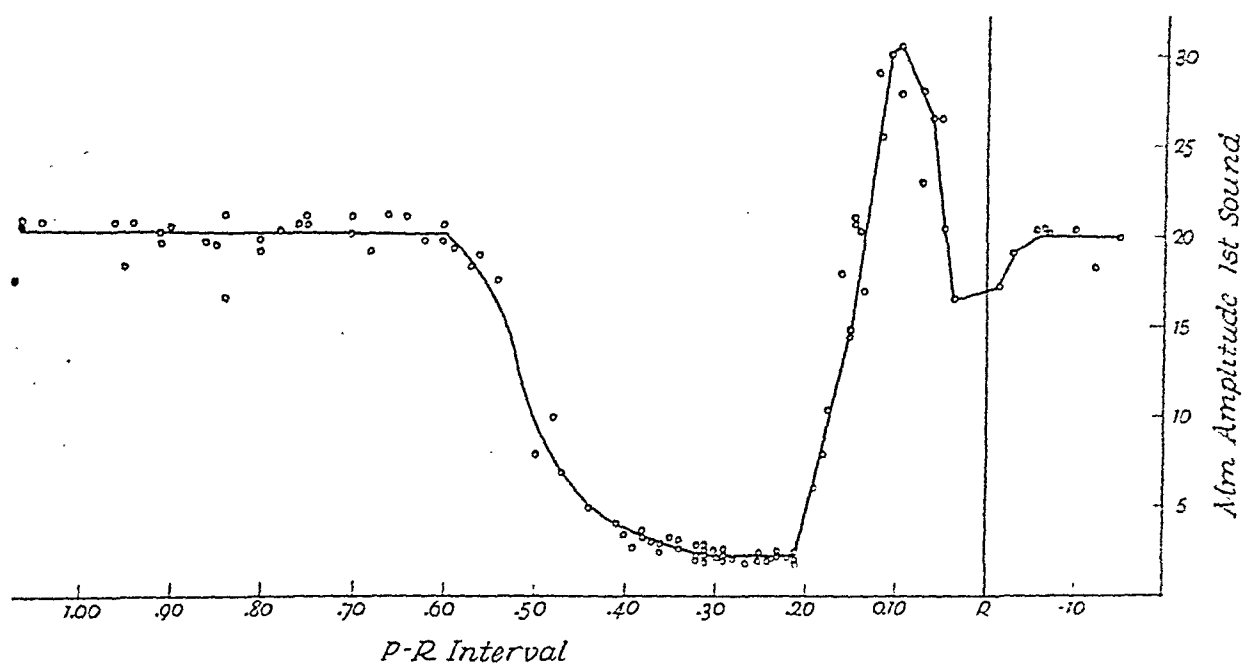
In Fig. 1, *A*, the amplitude of the first sound fell rapidly when the P-R interval was as short as 0.43 second, and sounds of minimal intensity were recorded at P-R intervals of 0.40 to 0.24 second. The intensity rose rapidly with shorter P-R intervals and reached a maximum at 0.11 second. It then fell off to a moderate value at about 0.04 second and rose again slightly as the P wave coincided with, or followed shortly after, the R wave.

The curve obtained after prostigmine (Fig. 1, *B*) differed only in the absence of conducted beats. Hence, the points expressing loudness of the first sound are lower when the P-R interval is shorter than 0.60 second, and are lowest at 0.21 second. Those for shorter P-R intervals are qualitatively identical with those in Fig. 1, *A*, though there happens to be fewer points in the region where the P-R interval was less than 0.09 second.

In Fig. 1, *A*, the curve rises acutely as the P-R interval exceeded 0.40 second. All points just above 0.35 second are associated with conduction of the P wave, and, hence, with a somewhat shorter R-R interval. This area should be compared with the corresponding area of Fig. 1, *B*. We have not attempted to evaluate the effect of varying R-R intervals.



A:



B.

Fig. 1.—A, Relationship of amplitude of first heart sound to preceding P-R interval. Case 1. B, Same as A after injection of prostigmine.

CASE 2.—J. C. S., a white man 25 years of age, had been under observation elsewhere since childhood for congenital heart disease. He had a systolic thrill and a systolic murmur maximal in the left third intercostal space, considered indicative of an interventricular septal defect. The heart was normal in size and there were no cardiac symptoms. A complete heart block, with normal intraventricular conduction, was present.

Fig. 2 shows the relationship between the amplitude of the first heart sound and the preceding P-R interval. With P-R intervals shorter than 0.54 second, the amplitude of the vibrations produced by the first heart sound diminished and reached a minimum at about 0.25 second. With shorter P-R intervals, the

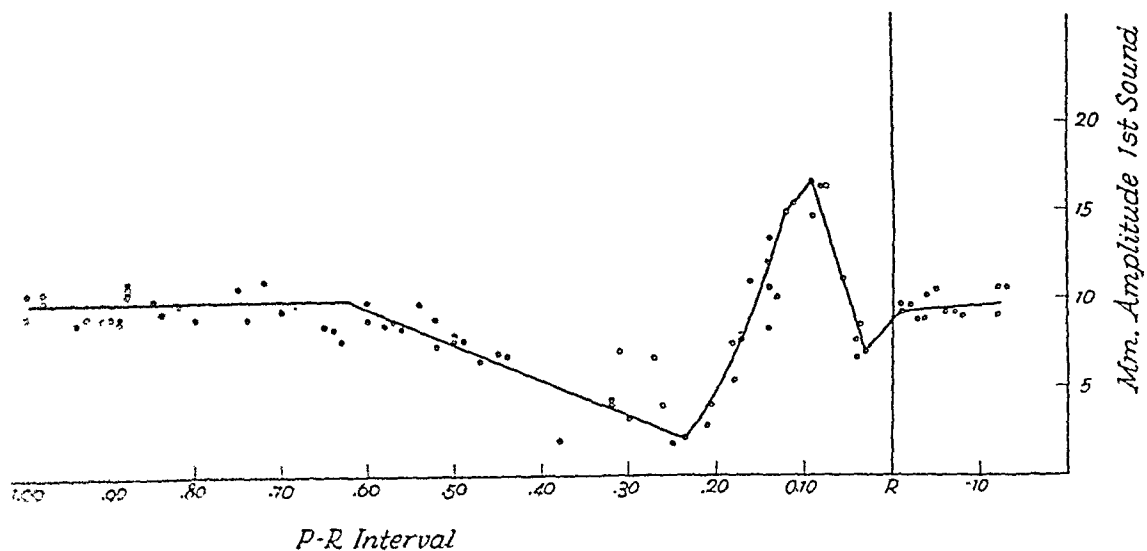


Fig. 2.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 2.

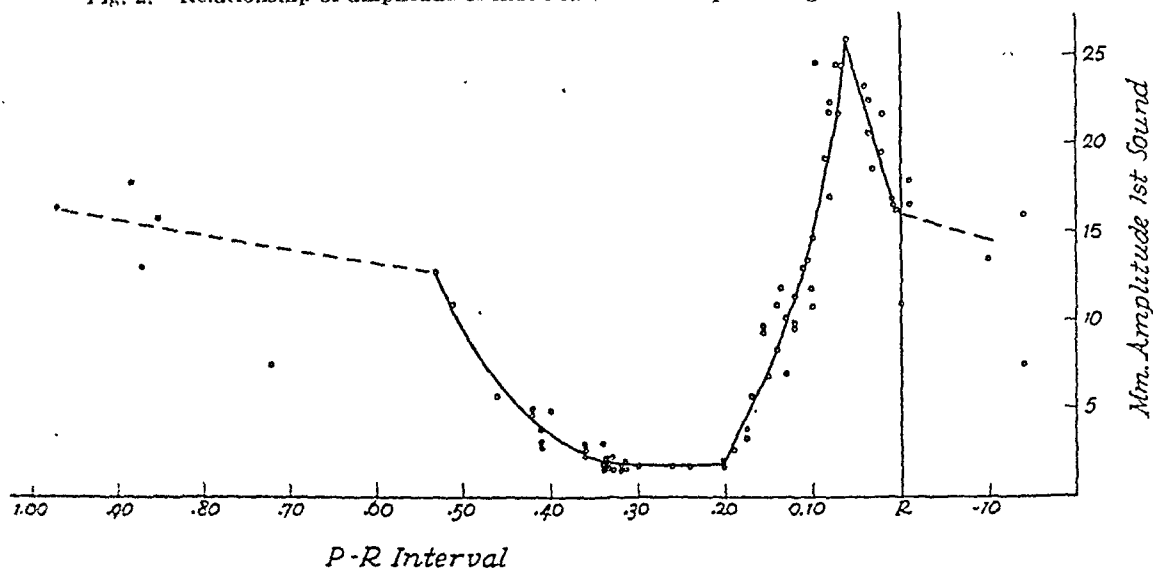


Fig. 3.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 3.

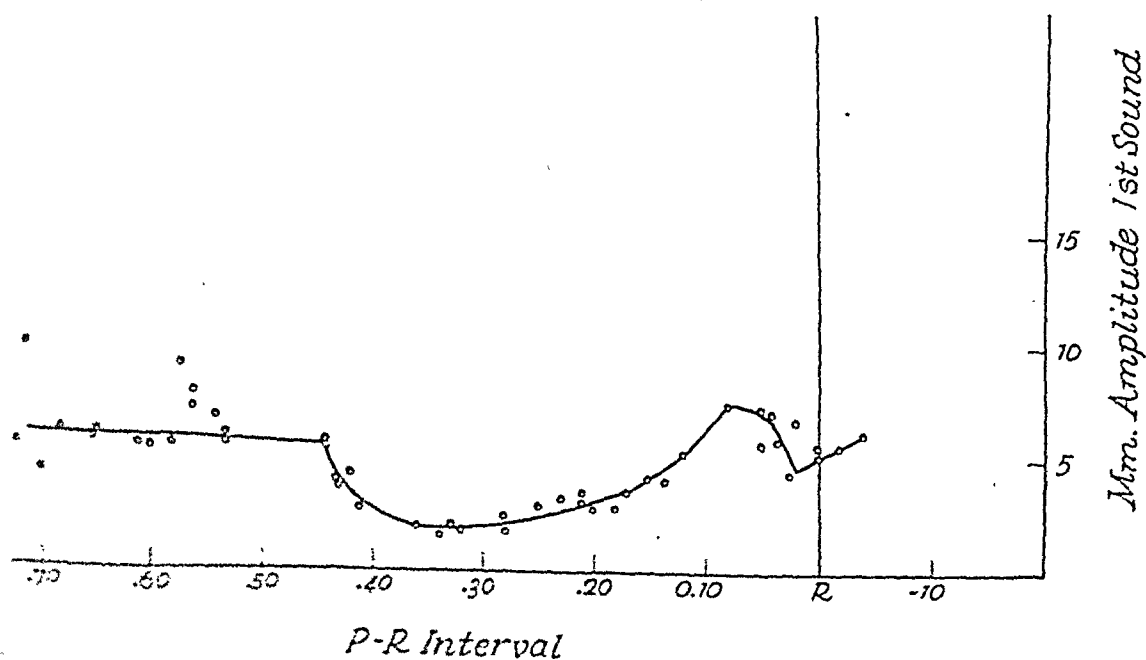


Fig. 4.—Relationship of amplitude of first heart sound to preceding P-R interval. Case 4.

amplitude increased, reaching a maximum value at approximately 0.09 second. A decrease followed with a secondary minimum at 0.04 second, with slightly higher values when the P wave coincided with, or followed shortly after, the R wave.

CASE 3.—L. C., a white girl 9 years of age, was sent to the hospital because of Adams-Stokes seizures. A very slow pulse rate had been noted at the age of 8 months, and syncopal attacks of varying severity and frequency had occurred since that age. These were readily controlled with small doses of ephedrine. The heart was enlarged; the apex was in the sixth intercostal space. A systolic murmur of moderate intensity could be heard at all valve areas, but was loudest at the pulmonary area. The electrocardiogram showed complete atrioventricular block; a left bundle branch block was usually present, but there was considerable variation in the contour of the QRS complexes.

Fig. 3 shows the relationship between the P-R interval and the amplitude of the following first heart sound. Very few points were obtained at P-R intervals greater than 0.53 second, and these were duplicates of instances where a short R-P interval could also be measured. With P-R intervals of less than 0.53 second, the loudness of the first sound diminished, and was at a minimum in the range 0.34 to 0.20 second. When the interval was shorter, the intensity of the sound rapidly increased, reaching a maximum at 0.06 second. It then diminished, with a secondary minimum apparently occurring when the P wave coincided with the R wave.

CASE 4.—M. C., a colored woman 53 years of age, presented herself at the clinic because of vertigo and edema of the ankles. She had experienced no definite syncopal attacks. The blood pressure was 250/150. The heart was dilated, with the apex in the anterior axillary line. There was a moderately loud systolic murmur heard over the whole precordium, loudest in the aortic and mitral areas. The electrocardiogram showed complete atrioventricular block and left bundle branch block. On one occasion transient auricular fibrillation was recorded.

Fig. 4 shows the data obtained in this study. The first heart sounds show, less prominently, the same variations in intensity noted in the preceding cases. The minimum amplitude occurred at about 0.36 to 0.28 second. This increased as the P-R interval shortened, and was at a maximum at 0.05 to 0.08 second. A secondary minimum occurred when the P-R interval was approximately 0.02 second.

COMMENT

Inspection of the data graphically recorded in the preceding material shows that there is a definite resemblance between the curves of all four cases. Two additional cases showed similar trends, but the points obtained were more widely scattered. Fig. 1, *B* may be assumed to be a fairly typical curve, particularly if it is supplemented by the points in the very short P-R interval range in Fig. 1, *A*.

The other curves are strikingly similar, with one exception. In Figs. 3 and 4, both derived from patients with left bundle branch block, the maximal intensity of the first heart sound definitely falls closer to the R wave by about 0.04 second. The secondary minimum in intensity of the sound in Figs. 1 and 2 occurs at 0.04 second. In Figs. 3 and 4, the corresponding points occur ap-

proximately simultaneously with the R wave. In other words, the presence of a left bundle branch block shifts the curve toward the R wave by about 0.04 second. This seems to agree with the conclusions reached by Wolferth and Margolies⁹ in their study of atrioventricular intervals and split first heart sounds. When there is left bundle branch block, the delay in excitation and in contraction of the left ventricle is reflected in the curves we have drawn, since left ventricular contraction is later after the beginning of the QRS complex than normal.

In their earlier paper, Wolferth and Margolies³ studied seven patients with defective A-V conduction. They related the P-R interval to the loudness of the first sound on a semiquantitative basis, classifying each sound in one of three categories of intensity. It is difficult to compare our measurements with data recorded simply as 1 to 3 plus intensity. Study of the tabulated data of Wolferth and Margolies shows that the maximum intensity of the first sound in their cases varied considerably from P-R intervals of 0 up to about 0.20 second. This at least agrees with our observation that the minimum intensity occurs usually in the range of P-R intervals of about 0.20 to 0.40 second. Attempts at more exact comparison seem fruitless.

Their classic study indicated strongly the vital importance of the position of the mitral leaflets in determining the loudness of the first sound. We believe that our own observations strongly support this opinion. It is, however, an unsettled question as to the exact position of the valve leaflets that produces a faint, or a loud, sound. This uncertainty caused Wolferth and Margolies not to accept valve closure as the most important factor in first sound production. They appear to lean toward the concept that a rapid rise in intraventricular tension, facilitated by already closed valves, produced the loudest first sound. They reasoned that, if the mitral leaflets were in a wide open position at the beginning of ventricular systole, slight regurgitation might occur, thus retarding the development of intraventricular tension and giving rise to first heart sound of relatively lower intensity. In this connection it is interesting to point out that all of our patients had mitral systolic murmurs varying from faint to moderate intensity. However, in the individual patient, there was no noticeable variation in the intensity or duration of the murmurs, either audibly or stethographically. Hence, while mitral regurgitation may have a contributory damping effect on the first heart sound, this effect may be considered consistent for all P-R intervals, and thus would not qualitatively affect the curves shown for our cases.

The only available experimental study of the movement of the mitral leaflets during the cardiac cycle is that of Dean.⁴ One of his curves is diagrammed in Fig. 5, A, and shows mitral valve movements during auricular systole. There is slight upward movement of the leaflets during the last moments of passive ventricular filling, followed by a sharp downward movement at the time of auricular contraction. The valve leaflets then move toward a position of incomplete closure; this is called auricular closure by Dean. They then drop downward again, but not as far as before.

Since the position of the mitral leaflets would appear to be a vital factor in determining the loudness of the first sound, we have attempted to compare our own data with the curve shown by Dean. Since (1) the amplitude of the vibrations of the first heart sound is clearly related to the interval between auricular and ventricular contraction, as indicated by the P-R interval, and (2) our data are graphed in such a manner that this interval is increased toward the left, it is necessary for comparison to reverse the diagram (Fig. 5, *B*), so that the times after auricular contraction are similarly increased toward the left. If one assumes that the loudest sound is produced when ventricular contraction suddenly tenses the mitral leaflets while they are in the widest open position, the further analysis of our graphs is facilitated by inverting the diagram, so that the position of closure is downward and the open position is upward. One then obtains Fig. 5, *C*, which should be compared with the curves graphed from our data.

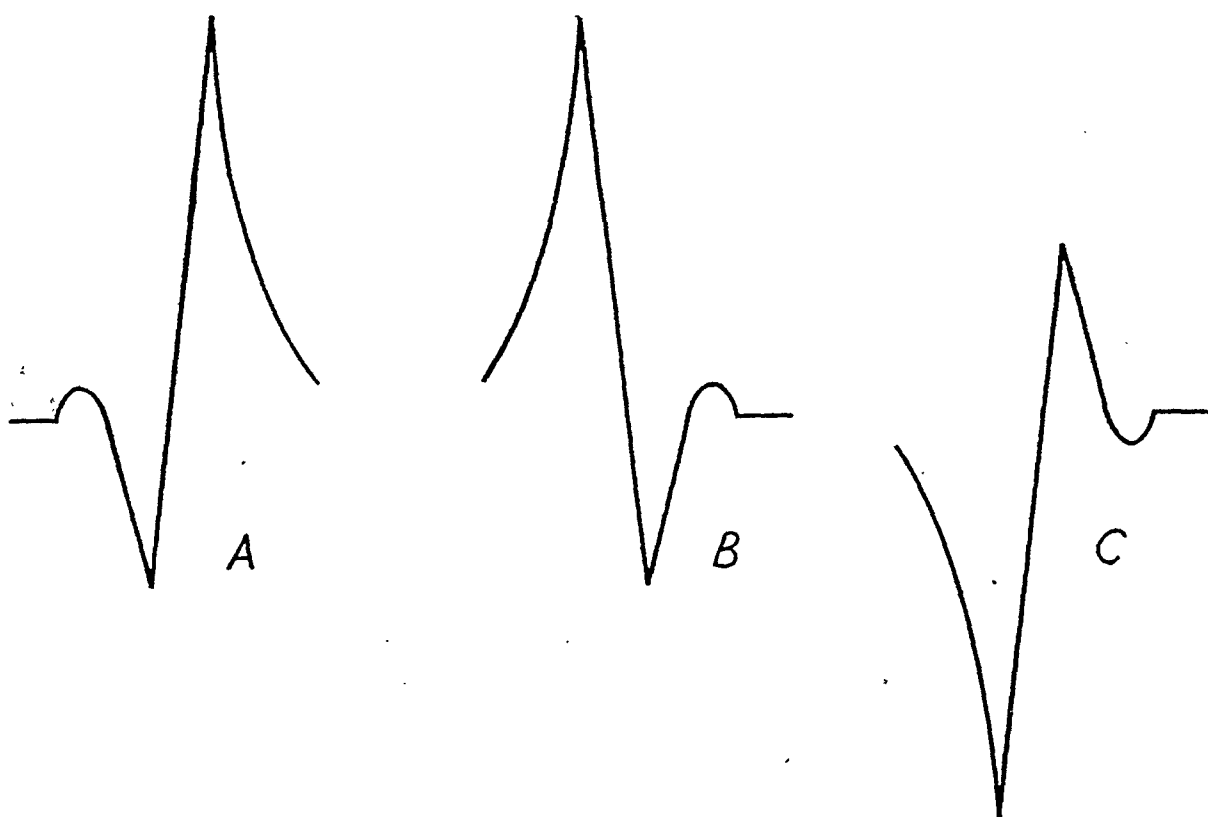


Fig. 5.—Movements of mitral valve due to auricular systole, represented according to Dean (*A*) and applied to our data (*B* and *C*). See text.

There are obviously many fallacies in an attempt to correlate information obtained experimentally from the cat heart with data on the intensity of human heart sounds. It seems to us that Dean's method possibly interfered with valve opening, and favored valve closure; nor is it easy to be certain of his time relationships since his figures do not include a time record. It is striking, however, that with appropriate recasting of his diagrams, figures are obtained which show substantial qualitative and semiquantitative agreement with our own. This agreement appears to support the contention of Dock⁵ that the loudness of the first sound depends on the degree to which the valves are open; valves nearly closed produce very faint sounds. This further emphasizes the dominant role

of the valve leaflets in the production of the sound, and minimizes the importance of muscular contraction as a primary factor in the production of the first heart sound.

The weak point in this hypothesis lies in the fact that the exact time-position relationship of the mitral leaflets remains undetermined. Some information may be gleaned from Dean's discussion, but it pertains to mechanical contraction of the heart chambers and mitral valve position. Hence, it cannot be profitably transferred to data associating the electrocardiographic complexes and heart sounds, even though these are directly related to contraction and valve position. In addition, application of time intervals from the cat heart to the human heart might be susceptible to considerable error. Hence, we have felt it futile to attempt to apply Dean's statements as to time to our own observations. It seems certain, however, as Dock⁵ has pointed out, that in the P-R interval range up to about 0.20 second, which includes the peak of loudness, the valves must be open rather than closed. This is more certainly true in the narrow range of 0.09 to 0.11 second where maximal sounds occur in those patients without bundle branch block. If this be accepted, the range of P-R intervals just above 0.20 second, where the first sounds are very faint, is that time interval where the valve leaflets are in the position designated by Dean as that of auricular closure.

These questions must await final agreement upon more exact information, in both experimental and human material, on the time-position relationships of the mitral leaflets. Such information should be obtainable by roentgen-kymographic technique in suitable patients, but we have been unable to find that any such study has been recorded.

SUMMARY

Four patients with complete atrioventricular block have been studied stethographically, and the loudness of the first heart sound related to the preceding P wave. Deductions have been drawn which emphasize the importance of vibrations of valvular origin in the production of the first heart sound.

REFERENCES

1. Griffith, T. W.: Remarks on Two Cases of Heart Block, *Heart* 3:143, 1912.
2. Orian, O., and Braun-Menendez, E.: *The Heart Sounds in Normal and Pathological Conditions*, London, 1939, Oxford University Press, p. 177.
3. Welferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse, *Arch. Int. Med.* 46:1048, 1930.
4. Dean, A. L.: The Movements of the Mitral Cusps in Relation to the Cardiac Cycle, *Am. J. Physiol.* 40:206, 1916.
5. Dock, W.: Mode of Production of the First Heart Sound, *Arch. Int. Med.* 51:737, 1933.
6. Dock, W.: Further Evidence for the Purely Valvular Origin of the First and Third Heart Sounds, *AM. HEART J.* 30:332, 1945.
7. Smith, J. R., Kountz, W. B., and Gilson, S. A.: A Consideration of the Extra Valvular Elements in the First Heart Sounds, *Proc. Soc. Exper. Biol. & Med.* 43:256, 1940.
8. Wiggers, C. J.: Factors Determining the Relative Intensity of the Heart Sounds in Different Auscultation Areas, *Arch. Int. Med.* 21:471, 1919.
9. Welferth, C. C., and Margolies, A.: The Influence of Varying As-Vs Intervals on Split First Heart Sounds: Its Bearing on the Cause of Split Sounds and the Mechanism of the First Sounds, *J. Clin. Investigation* 14:605, 1935.

AN ELECTROCARDIOGRAPHIC PATTERN OF INFARCTION OF THE INTERVENTRICULAR SEPTUM, EXTENDING FROM THE ANTERIOR TO THE POSTERIOR ASPECT OF THE HEART

HUGO ROESLER, M.D., PHILADELPHIA, PA., AND
WILLIAM DRESSLER, M.D., NEW YORK, N. Y.

THE use of multiple chest leads has enhanced our ability to diagnose accurately the site of myocardial infarction.¹ Anteroseptal location is indicated by significant changes in the leads from the right side of the precordium. These signs, however, are not dependable evidence of involvement of the interventricular septum. They may be also observed when infarction is confined to parts of the anterior wall close to the septum. Similarly, when a Q_3 - T_3 pattern is present, infarction of the posterior wall may or may not include a portion of the interventricular septum. There are, however, cases showing a combination of the Q_3 - T_3 pattern and significant changes in the leads from the right side of the precordium which suggest infarction of the same stage in the anterior and posterior walls. Wilson and associates,¹ who published such a tracing in 1944, remarked, "We are unable to explain these findings but may point out that apical infarction may give rise to electrocardiographic changes of this sort if the heart were in the vertical position." More recently Wilson and associates² published a case of this type in which necropsy revealed a myocardial infarction that extended from the anterior wall through the interventricular septum to the posterior wall of the left ventricle.

In the last few years we have had an opportunity to observe five cases, with necropsy control, whose electrocardiograms showed the Q_3 - T_3 pattern and changes in the chest leads significant of anteroseptal infarction. All cases presented a rather identical anatomic finding. The interventricular septum was infarcted throughout between the anterior and posterior aspects of the heart, while involvement of the anterior and posterior walls varied from case to case.

CASE REPORTS

CASE 1.—N. E., a 44-year-old woman, was suddenly seized with precordial pains that radiated to both arms on June 25, 1945. The pain persisted for hours and was accompanied by vomiting. It was followed by rise in temperature and an increase of the white blood count and sedimentation rate. Gallop rhythm was heard over the heart. The blood pressure was 150/108. On the ninth day after the attack of pain, the patient succumbed to cerebral embolism.

From the Departments of Medicine and Radiology, Temple University Hospital and Medical School, Philadelphia, Pa., and the Department of Medicine, Israel Zion Division, Maimonides Hospital, Brooklyn, N. Y.

Received for publication Feb. 18, 1947.

An electrocardiogram (Fig. 1, *A*) was taken seven hours after the onset of the attack of pain. It showed significant Q waves in Leads II and III. QRS was of low voltage in the limb leads; its duration was 0.08 second. The S-T junction was depressed in Lead I and elevated in Lead III. T_2 was dome-shaped. In Leads CF_2 and CF_3 the S-T junction was abnormally elevated and the T wave was high. Tracing *B* (Fig. 1), which was taken three days after *A*, showed progressive changes in limb and chest leads. The duration of QRS was increased to 0.12 second and the tracing showed the pattern of right bundle branch block. The Q deflection was more pronounced in Leads II and III. T_2 had the features of a "coronary T." In Leads CF_2 and CF_3 the S-T junction was still elevated and there was beginning inversion of T.

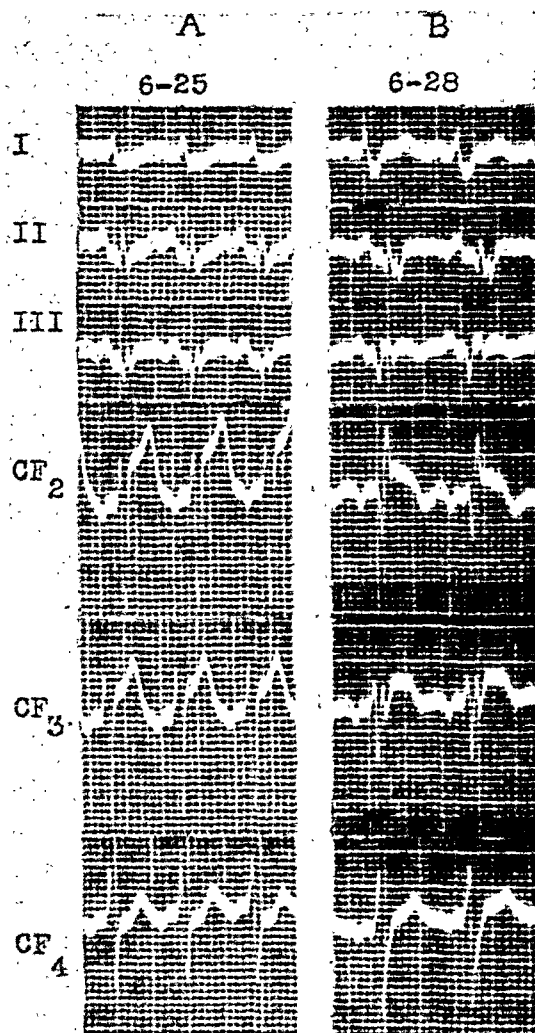


FIG. 1.—Case 1. Extensive recent infarction of the interventricular septum, involving its entire length and extending posteriorly over the apical portion of the left ventricle. The electrocardiograms, taken seven hours and three days, respectively, after the coronary attack, show progressive changes indicative of acute posterior and anteroseptal infarctions.

Progressive electrocardiographic changes in the limb leads pointed to acute posterior wall infarction; those in Leads CF_2 and CF_3 suggested acute infarction of anteroseptal site.

Post-mortem examination revealed marked narrowing of the coronary arteries due to arteriosclerosis. The mid-portion of the right coronary artery was occluded by a recent thrombus. A fresh infarction occupied the entire length of the interventricular septum and extended posteriorly over the apical portion of the left ventricle. Both endocardial surfaces of the interventricular septum were covered with organizing blood clots.

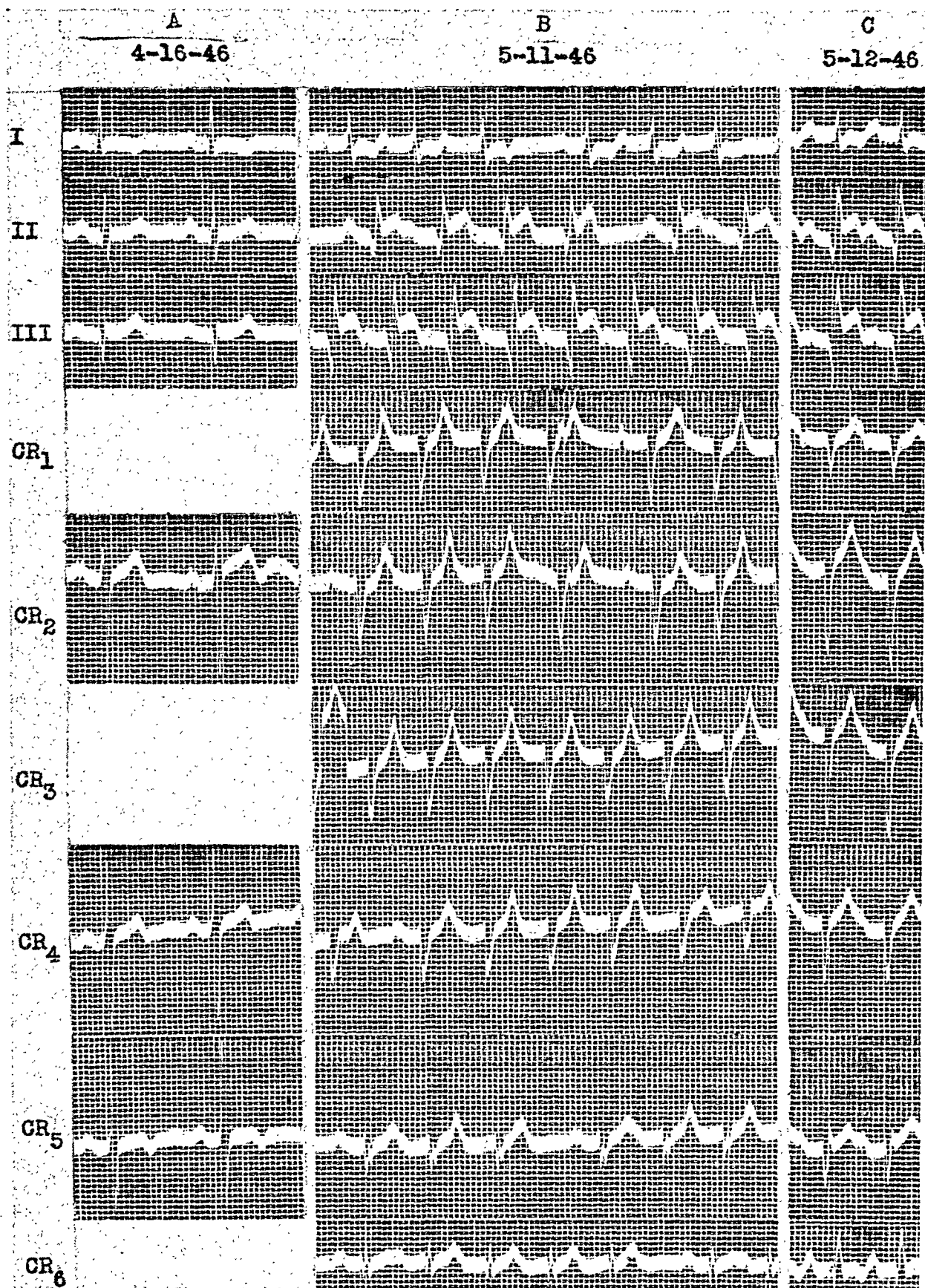


Fig. 2.—Case 2. Recent infarction involving the whole length of the interventricular septum, its entire width in the apical region, and portions adjacent to the septum in the anterior and posterior walls of the left ventricle. Small old anterolateral infarction. A, Before the severe coronary attack. Inversion of T in Leads I, CR₄, and CR₅, suggestive of damage in the anterolateral wall. B and C, Two and three days, respectively, after an attack suggestive of acute coronary obstruction. Signs of acute posterior infarction in the limb leads and of extensive anterior infarction in the chest leads. The leads from the right side of the precordium show more pronounced changes than the leads from the left side.

Summary.—Progressive electrocardiographic changes in the limb leads and in the chest leads from the right side pointed to acute infarction involving the posterior aspect and the antero-septal walls of the left ventricle. Necropsy revealed a recent infarction which occupied the entire length of the interventricular septum, and extended posteriorly over the apical portion of the left ventricle.

CASE 2.—F. M., a 71-year-old man, suffered from angina of effort for the past seven years, but never had a prolonged attack of chest distress. When he was first examined on April 16, 1946, there were no abnormal cardiac findings on physical examination. An electrocardiogram (Fig. 2, A) showed inversion of T in Leads I and CR₅, and a diphasic T wave in CR₄. These changes suggested damage probably in the lateral wall of the left ventricle. On May 9, 1946, the patient suffered a prolonged attack of epigastric pain with nausea and pulmonary edema. After the attack the blood pressure was 80/50 and the heart rate was 138 per minute. The patient died on May 16, 1946.

An electrocardiogram (Fig. 2, B), which was taken two days after the attack of pain, showed sinus tachycardia with second degree A-V block. In Leads II and III there were prominent Q waves and marked elevation of the S-T junction. The R deflection was absent in Leads CR₁ and CR₂ and was abnormally small in the other chest leads. In Lead CR₆ a small Q wave preceded an R deflection of low voltage. Tracing C, taken a day after B, differed only slightly from the previous tracing. In Lead CR₆ the R deflection was larger and was followed by a "coronary T." The changes in the limb leads pointed to acute posterior wall infarction; the changes in the chest leads, which were more pronounced in leads from the right of the precordium, indicated infarction of the antero-septal area extending rather far toward the left.

Post-mortem examination revealed narrowing of the coronary arteries in multiple spots due to arteriosclerosis. A marked stenosis was present in both the anterior and posterior descending branches at a point about 1 cm. from their origin. The main stem of the right coronary artery was occluded by a fresh thrombus. A large recent infarction extended through the whole length of the interventricular septum and involved its entire width in the apical region. There, the infarction extended over the anterior and posterior surfaces of the right and left ventricles adjoining the septum for a distance of about 2 cm. in the right ventricle and for double that distance in the left ventricle. At the left lateral contour in the apical region a slight bulge, about 2.5 cm. in diameter, was observed; it was formed by scar tissue, the remnant of an older infarction.

Summary.—The electrocardiographic changes suggested acute infarction of the posterior wall and involvement of the antero-septal wall of the left ventricle. Post-mortem examination showed a recent infarct which occupied the whole length of the interventricular septum and its entire width in the apical region. From the septum the infarction extended over the anterior and posterior walls of both ventricles, occupying an area 2 cm. wide at the right of the septum and an area double that size to the left of the septum. A small, old infarction was present at the anterolateral aspect of the apical region.

CASE 3.—E. P., a 54-year-old woman, was admitted to the hospital in the beginning of 1942 for treatment of diabetes. Her heart was found to be enlarged. The blood pressure was 210/130. An electrocardiogram (Fig. 3, A) showed signs suggestive of left ventricular hypertrophy.

During the last two weeks of November, 1942, the patient complained of shortness of breath on exertion. On the evening of Dec. 1, 1942, she experienced pressure in the precordial region for an hour. On the next morning, while walking to the diabetic clinic, she became prostrated and sweated profusely. An electrocardiogram taken on that day (Fig. 3, B) showed decrease

of the R deflection in the limb and chest leads. Also, an inverted T with symmetrical limbs was noted in Leads I and CF₅. In Leads CF₃ and CF₄ the S-T junction was elevated and the T wave was semi-inverted. These changes corroborated the impression gained from the history that the patient had suffered a coronary attack with resulting damage to the anterior wall of the heart. An electrocardiogram (Fig. 3, C) taken a week after B, showed but slight changes. In Lead CF₃ the R wave had become very small and inversion of T was less pronounced; there was sharp inversion of T in Leads CF₄ and CF₅.

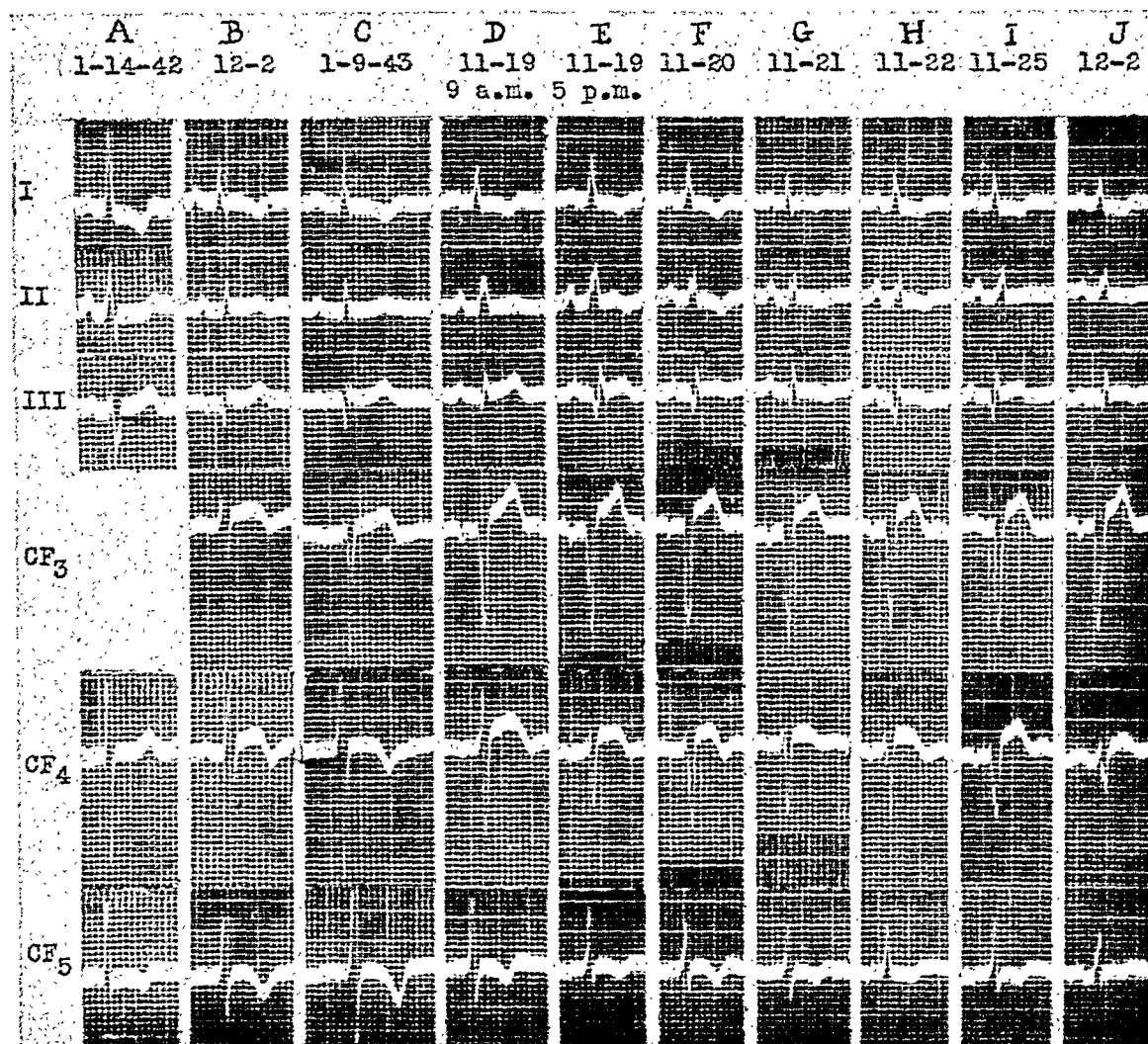


Fig. 3.—Case 3. Recent infarction of the lower part of the interventricular septum, merging with small areas of infarction in the anterior and posterior walls of the left ventricle. A, Before the severe coronary attack. Signs suggestive of left ventricular hypertrophy. B and C, After a minor coronary attack in November, 1942. Signs of damage in the anterior wall. D through J, Following a severe coronary attack on Nov. 19, 1943. Signs of posterior and anteroseptal infarction with little tendency toward progressive changes.

On the morning of Nov. 19, 1943, the patient again suffered an attack of severe substernal tightening and was admitted to the hospital. She was in shock and presented signs of pulmonary congestion. An electrocardiogram taken on that day (Fig. 3, D) showed a small Q wave in Lead III and decrease of the amplitude of R in the chest leads. The S-T junction was elevated in Leads III, CF₃, and CF₄. T₂ was dome-shaped; the amplitude of T₃ had increased. There was also an increase in the voltage of T in CR₃ and CR₄. The next tracing (Fig. 3, E), which was taken eight hours after D, showed further changes: Q₃ was broader and deeper; there was terminal inversion of T₂ and T₃; in Lead CF₄ the amplitude of R had further decreased, and there was abnormal elevation of the S-T junction, coupled with inversion of T.

The patient developed low-grade fever and leucocytosis. The signs of pulmonary congestion persisted. Serial electrocardiograms taken on November 20, 21, 22, 25, and on December 2 (Fig. 3, *F-J*) showed little tendency to change. In Leads III, CF_3 , and CF_4 , the S-T junction remained elevated and there was little progress toward complete inversion of T. Death occurred on Dec. 8, 1943.

Post-mortem examination revealed marked arteriosclerosis of the coronary arteries. The lumina of the posterior descending and right marginal branches were reduced to pin-point size. The distal ramifications of the anterior descending branch were almost completely obliterated. An area of recent infarction, measuring 2.0×1.5 cm., was found at the base of the posterior wall. It merged with a recent infarction of the interventricular septum, which extended through the lower half of the septum toward the anterior aspect of the heart and merged there with a recent infarction in the apical area, which measured 2.5×1.0 centimeters.

Summary.—A minor coronary attack in November, 1942, had resulted in damage to the anterior wall, as indicated by the electrocardiogram. Following another attack in November, 1943, the electrocardiogram showed signs of infarction in Leads II and III and in leads from the right side of the precordium. Post-mortem examination revealed a recent infarct which occupied the lower part of the interventricular septum and merged with small areas of infarction, apparently of the same age, in the anterior and posterior walls of the left ventricle.

CASE 4.—S. E., a 55-year-old woman, had diabetes and hypertension for many years. On Jan. 11, 1942, she was seized with crushing pain in the precordial region and left shoulder. The attack lasted for several hours. It was followed by fever and increase of the white blood count and sedimentation rate.

An electrocardiogram was available which had been taken in 1939, two and one-half years prior to the pain attack (Fig. 4, *A*). It showed signs suggestive of left ventricular hypertrophy. A tracing taken two days after the attack (Fig. 4, *B*) showed significant changes. In Lead II there was a prominent Q deflection; the S-T junction was elevated; the S-T segment upward-convex; and the T wave semi-inverted. In Lead IV F the R deflection had disappeared, the S-T segment was elevated, and the T wave was sharply inverted. Another electrocardiogram, taken eight days after the attack (Fig. 4, *C*) showed even more pronounced elevation of S-T in Leads II and III, and straightening of the S-T segment in Lead III. In the following two tracings (*D* and *E*) progressive inversion of T in Leads II and IV F was noted.

The patient suffered two more attacks of prolonged precordial pain in April, 1942. However, the electrocardiogram (Fig. 4, *F*) showed only regressive changes of T. Death occurred on April 26, 1942.

Post-mortem examination revealed diffuse arteriosclerosis of the coronary arteries. The anterior descending branch was occluded by a recent thrombus about 2 cm. from its origin. Below the point of recent occlusion, there was almost complete obliteration of the lumen due to the arteriosclerotic process. The left circumflex and the posterior descending branches were moderately narrowed. The weight of the heart was 520 grams. The lower half of the left ventricle was thinned out and showed slight aneurysmal dilatation. The myocardium of the entire lower half of the interventricular septum was replaced by fibrous tissue which merged with scar tissue in the anterior wall of the left ventricle. In addition there was a recent infarction which involved the lower part of the posterior and lateral walls of the left ventricle.

Summary.—There had been two coronary attacks; one three and one-half months and the other two and one-half weeks prior to death. After the first attack, the electrocardiogram showed a Q_3 - T_3 pattern and significant changes in Lead IV F, suggesting acute posterior and anterior infarctions. Although

only one chest lead was available, absence of significant changes in Lead I suggested an anteroseptal rather than an anterolateral site of infarction. These electrocardiographic changes obviously corresponded to the older, healed infarction which was revealed by necropsy. It occupied the entire lower half of the interventricular septum and an adjacent portion of the anterior wall of the left ventricle.

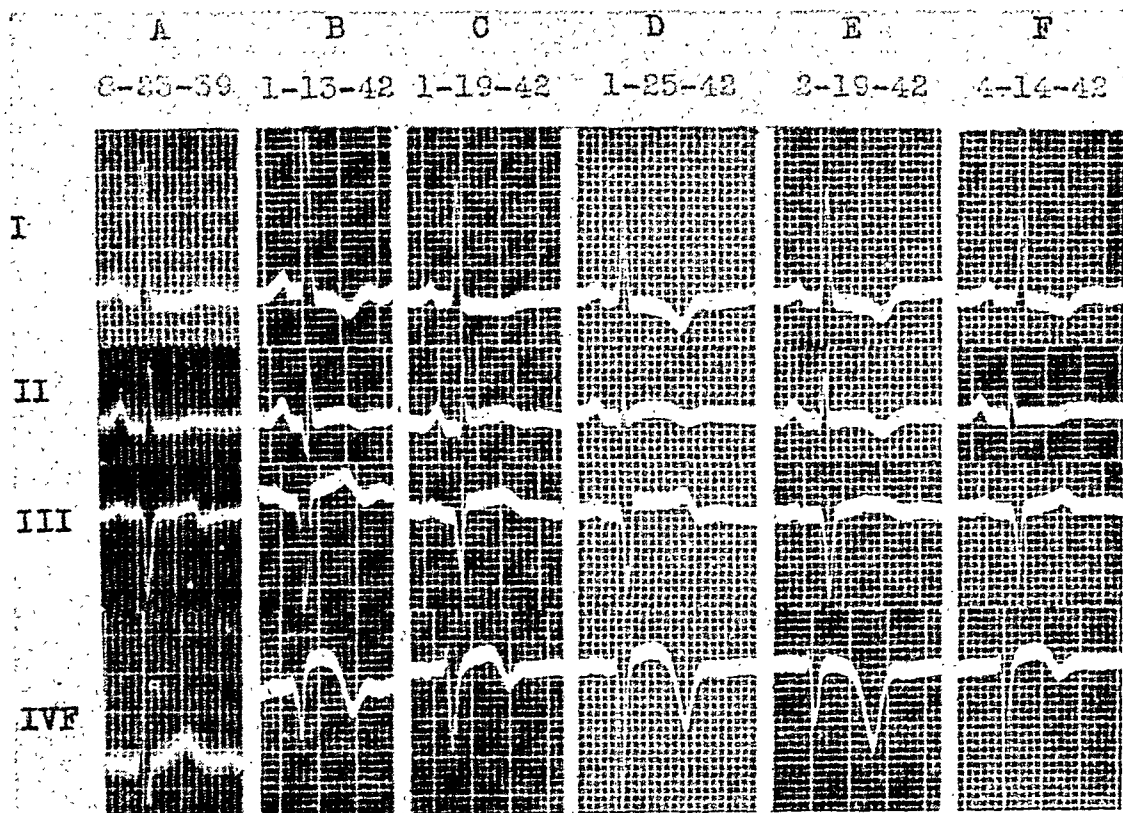


Fig. 4.—Case 4. Healed infarction occupying the lower half of the interventricular septum and an adjacent portion of the anterior wall of the left ventricle. Recent infarction involving the lower part of the posterior and lateral walls of the left ventricle. A, Before the severe coronary attack. Signs suggestive of left ventricular hypertrophy. B through E, Two days after a severe coronary attack. Signs of posterior and anterior infarction; progressive changes. F, After two new attacks of prolonged chest pain; no significant changes.

CASE 5.—E. S., a 69-year-old man, complained of substernal tightness on exertion for the past several years. Three weeks prior to admission to the hospital, the patient suffered an attack of "gas pain across the back." This was followed, five days before admission, by a more severe attack of chest pain which was relieved by morphine. The patient was admitted to the hospital on Jan. 17, 1939. After the second attack, the blood pressure dropped to 86/62. The heart sounds were distant and a pericardial friction rub was heard. Low-grade fever and leucocytosis developed. Death occurred nine days after the second attack.

An electrocardiogram (Fig. 5) was taken on Jan. 17, 1939, five days after the second attack of severe pain. It showed a Q_3 - T_3 pattern and changes suggestive of anteroseptal infarction in Leads CF_2 and CF_4 .

Post-mortem examination revealed stenosis of the coronary arteries due to arteriosclerosis which was most marked in the anterior descending branch. There was a huge recent infarction which involved almost the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle. Posteriorly, the infarction extended for about 0.5 cm. to the right of the septum.

Summary.—The electrocardiogram showed changes significant of posterior and anteroseptal infarction. Post-mortem study revealed a huge recent infarct that occupied nearly the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle; posteriorly, a very narrow strip to the right of the septum was involved.

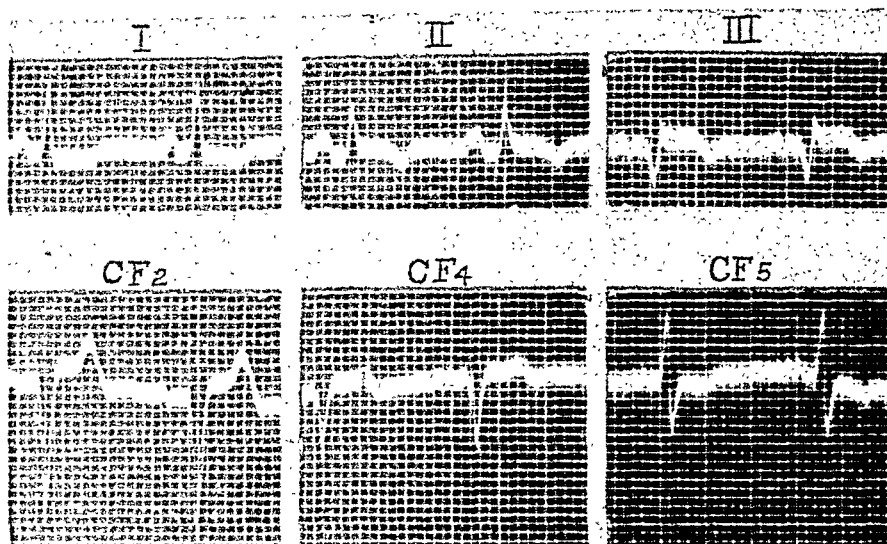


Fig. 5.—Case 5. Recent infarction occupying almost the entire lower two-thirds of the interventricular septum and an adjoining area of the anterior wall of the left ventricle, extending posteriorly for 0.5 cm. to the right of the septum. Five days after the coronary attack, the electrocardiogram shows signs of posterior and anteroseptal infarction.

COMMENT

All cases in this report showed electrocardiographic signs of both posterior and anterior wall infarction. Where multiple chest leads were available (Cases 1, 2, 3, and 5), an anteroseptal site of infarction was indicated by significant changes in leads from the right side of the precordium as far as Position C₄. In Case 4 only one chest lead (IV F) was taken and it showed signs of anterior infarction. Since significant changes were absent in Lead I, which usually reflects changes of potential in the left lateral wall, an anteroseptal rather than a lateral site of the infarction was suggested. Progressive changes in limb and chest leads were observed in Cases 1, 3, and 4; this indicated that posterior and anterior infarctions were of recent origin and of approximately the same age.

In all cases, infarction of the interventricular septum was the outstanding post-mortem finding. In three instances the infarction was very extensive, occupying either the whole length of the septum (Cases 1 and 2) or almost the entire lower two-thirds of the septum (Case 5). In two cases (Cases 3 and 4) the lower half of the interventricular septum was the site of infarction. In all instances, the infarction extended from the anterior to the posterior aspect of the heart, encroaching upon a portion of either the anterior (Case 4) or posterior wall (Case 1), or both (Cases 2, 3, and 5).

In the case published by Wilson and associates,² it was not revealed how large a portion of the septum was involved. In a drawing of a cross section of

the heart, it was indicated that the infarction extended from the anterior wall through the septum to the posterior wall of the left ventricle. Wolferth and Wood³ reported cases of "acute cardiac infarction involving anterior and posterior surfaces of the left ventricle." Signs of acute infarction were present in Leads II and III and in chest leads taken from the apical area. Three of their cases were necropsied. In one (Case 1) the autopsy report stated that "the interventricular septum was almost completely infarcted" in addition to portions of the anterior and posterior walls of the left ventricle. In their Case 11, an infarction involved the lower half of the interventricular septum and parts of the anterior and posterior walls of the left ventricle. In Case 2 an aneurysm was found at the posterior wall which merged with fibrotic changes in the anterior apical portion of the left ventricle. No mention was made of involvement of the interventricular septum. Clapper, Myers, and Oren⁶ reported on cases of myocardial infarction involving the anterior and posterior aspects of the apex of the left ventricle. The electrocardiogram showed a Q_3 - T_3 pattern and significant changes in the chest leads from Positions C_3 and C_4 .

References to septal infarction are scarce in the literature. In our search for pertinent cases, we examined reports on rupture of the interventricular septum secondary to myocardial infarction. Unfortunately, the majority of the considerable number of case reports includes either no electrocardiogram or only the three standard leads. We found only two cases in which, in addition to the standard leads, Lead IV F was available.^{4,5} Both cases showed the Q_3 - T_3 pattern and significant changes in Lead IV F. In one case⁴ a ventricular aneurysm was present and the post-mortem report stated that "the aneurysm, in addition to involving the apical third of the interventricular septum, extended upward from the apex on to the anterior left ventricular wall for a distance of 4.5 cm., and upward from the apex on the posterior left ventricular wall for a distance of 1.5 cm." In the other case of ruptured interventricular septum,⁵ the post-mortem examination revealed an "infarction of the lower half of the interventricular septum and the immediately adjacent anterior apical portions of the left ventricle."

The findings in the literature are in accord with our own observations concerning the significance of the Q_3 - T_3 pattern which is combined with signs of anterior (anteroseptal) infarction.

It should be mentioned that Wilson has pointed out that infarction of the interventricular septum is indicated in cases of left bundle branch block by the presence of significant Q waves in the chest leads. We were able to confirm this view on the basis of post-mortem findings in two cases which showed these electrocardiographic features.

SUMMARY

Five cases are reported which presented in the limb leads signs of posterior wall infarction and, simultaneously, in the precordial leads, signs of anteroseptal infarction. Post-mortem examination showed in all cases infarction of the interventricular septum that extended from the anterior to the posterior aspect

of the heart and involved variable portions of the anterior or posterior wall adjacent to the septum. Similar cases are quoted from the literature.

It is suggested that extensive infarction of the interventricular septum, reaching from the anterior to the posterior aspect of the heart, be considered when the electrocardiogram shows a Q_3 - T_3 pattern and diagnostic signs of infarction in leads from the right side of the precordium, and when the changes in the limb and chest leads indicate the same stage of acute or subacute infarction. A similar electrocardiographic pattern sometimes is observed when infarction in the apical region extends from the anterior to the posterior aspect of the heart.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Pre-cordial Electrocardiogram, *AM. HEART J.* 27:19, 1944.
2. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, *AM. HEART J.* 32:277, 1946.
3. Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, *Arch. Int. Med.* 56:77, 1935.
4. Bayley, R. H., and Fader, D. E.: Ante-mortem Diagnosis of Rupture of the Interventricular Septum as a Result of Myocardial Infarction; Report of a Case, *AM. HEART J.* 21:238, 1941.
5. Weber, M. L.: Perforation of the Interventricular Septum Following Infarction; Intra-vitam Diagnosis, *Ann. Int. Med.* 19:973, 1943.
6. Clapper, M., Myers, G. B., and Oren, B. G.: The Electrocardiographic Diagnosis of Infarction of the Anterior and Posterior Aspects of the Left Ventricle, *Proc. Am. Federation Clin. Research* 2:45, 1945.

MYOCARDITIS

A CLASSIFICATION OF 1402 CASES

IRA GORE, LIEUTENANT COLONEL, MEDICAL CORPS, ARMY OF THE UNITED STATES,
AND OTTO SAPHIR, M.D.,* RESIDENT CONSULTANT, ARMY

INSTITUTE OF PATHOLOGY

WASHINGTON, D. C.

THE autopsy material submitted to the Army Institute of Pathology during the recent war contained an unusually large number of cases of myocarditis. In view of current interest in this subject aroused by the reports of transitory electrocardiographic alterations in a number of different diseases, a review of this wealth of material was considered important in determining an anatomic background for such changes. A total of 1,402 cases of myocarditis verified by pathologic examination was available for review.

The clinical diagnosis "myocarditis" fell into disrepute in the early part of this century following a period in which it had been used indiscriminately to designate any cardiac disorder not accompanied by an organic murmur. Naturally, many instances of hypertensive and arteriosclerotic heart disease were misdiagnosed. It became almost axiomatic, therefore, to state that myocarditis for all practical purposes did not exist, except as a result of rheumatic fever and diphtheria. Although such a view undoubtedly has had a beneficial effect on accuracy of diagnosis and augmented knowledge of heart diseases, it would appear that, since hypertensive and arteriosclerotic heart disease are so thoroughly recognized, this working rule has served its clinical usefulness and had better be discarded. Further perpetuation of the idea it embodies will only serve to hinder progress. To have followed such a rule would have prevented recognition of myocarditis in 75 per cent of the cases making up the material on which this report is based; and as a matter of fact, the records show the correct diagnosis was rarely made.

In recent years considerable interest has been aroused by the publication of a number of case reports of Fiedler's (idiopathic, or isolated) myocarditis. The clinical records not infrequently refer to an acute febrile illness shortly antecedent to, or coincident with, the onset of the cardiac disorder. To assay the significance of such acute illnesses in relation to cardiac symptoms, it was necessary to review not only a large number of cases of myocarditis, but also to ascertain the incidence of carditis in various acute diseases. Saphir¹ made such a review in 1941, reporting a series of 240 cases of myocarditis encountered in 5,626 consecutive au-

Received for publication April 9, 1947.

*Pathologist, Michael Reese Hospital, Chicago, Ill.

topies. One hundred eighty-six of the reported cases were nonrheumatic, and in a distressing proportion the myocarditis had gone unrecognized by the clinicians who had studied the cases in life. Similar observations can be made on the 1,402 cases accumulated at the Army Institute of Pathology. There were only 130 cases of rheumatic carditis, so that the heart condition in more than 90 per cent of the series was nonrheumatic. Clinically, myocardial involvement had not been suspected in the majority of these. The proportion of missed diagnoses becomes still more impressive if the diphtheria cases, constituting approximately 10 per cent of the total, are excluded; but for that matter, the cardiac complication was recognized in only one-third of them.

The diagnostic failure can not be attributed to an absence of signs or symptoms. The clinical records frequently mention cyanosis, dyspnea, and orthopnea. A significant degree of hypotension was often observed, and with it a weak, feeble, or thready pulse. Often the recorded pulse rate and temperature showed a loss of the normal ratio. Sometimes chest pain, characterized by substernal oppression or discomfort, was observed. Electrocardiograms, in the majority of instances in which they were taken, disclosed evidence of myocardial damage. Manifestations of congestive heart failure, which occurred in an appreciable number of cases, included distended neck veins, serous effusions, swollen tender liver, and dependent edema. Unexpected deaths were numerous, and in the small group of patients who survived for periods ranging from one to six months, embolic phenomena were observed.

The importance of overcoming the prevailing prejudice against the diagnosis of myocarditis is well demonstrated in a review of the available records of scrub typhus fever. The clinical recognition of myocarditis in this disease became more frequent as the initially inexperienced physicians became aware of the remarkably high incidence of carditis encountered in fatal cases. Needless to say, there had been no change in the clinical manifestations observed but merely an increased awareness of them and a more accurate evaluation of their significance.

Table I is included to indicate the wide variety of diseases and conditions that were found associated with the myocarditides encountered in this series. The known etiological agents include: toxic substances (diphtheria); physical or chemical agents (heat stroke and carbon monoxide poisoning); various specific virus, rickettsial, spirochetal, and fungus diseases; less specific infectious processes; and various metabolic states such as inanition and hypersensitivity. It would be a mistake to conclude that such a grouping is sharp and distinctive. For example, it is impossible to evaluate properly the effects of absorbed toxins, bacterial infections, and treatment in the myocarditis associated with burns, or of secondary bacterial infections so frequently complicating primary virus diseases. Nor are these the only conditions in which other infectious processes interfere with analysis of the cardiopathic effect; only six of the thirty-three cases of starvation associated with myocardial inflammation could not be related to a coexistent infectious process. In other diseases, such as infectious mononucleosis, acute infectious polyneuritis (Guillain-Barré syndrome), and Boeck's

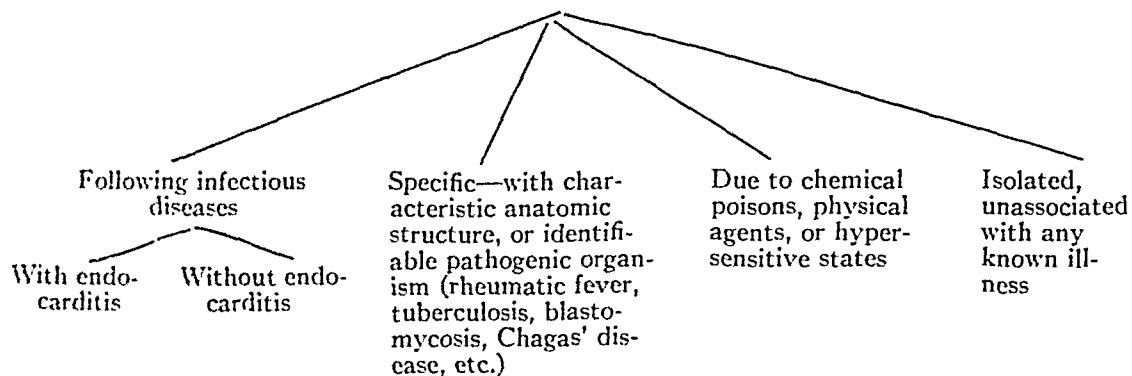
TABLE I. DISEASES ASSOCIATED WITH MYOCARDITIS*

	COLUMN 1	COLUMN 2		COLUMN 1	COLUMN 2
Rickettsial diseases	227	227	Septicemia	11	23
Scrub typhus	23	48	Streptococcus	34	107
Epidemic typhus	9	19	Staphylococcus	9	18
Rocky Mountain spotted fever	144	221	Pneumococcus	15	Unknown
Diphtheria	208	208	Other acute bacteremias		
Subacute bacterial endocarditis	130	130	Acute glomerulonephritis	14	160
Rheumatic heart disease	111	256	Acute tonsillitis	12	Unknown
Meningococcemia	24	44	Acute nasopharyngitis	41	Unknown
Scarlet fever	7	8	Cellulitis, lymphangitis, and wound infections	13	Unknown
Weil's disease	6	11	Tularemia	1	16
Relapsing fever	2	66	Brucellosis	2	4
Syphilis (gummatous)	1	1	Miscellaneous (postinfectious)	13	Unknown
Chagas' disease	5	41	Exfoliative dermatitis	7	44
Schistosomiasis	5	135	Arsenical reaction	1	18
Malaria	2	2	Sulfonamide hypersensitivity	105	Unknown
Trichinosis	13	144	Disease unknown (so-called "idiopathic")	43	
Acute encephalitis	13	94	Starvation	33	50
Polio myelitis	13	9	Heat stroke		
Infectious mononucleosis	6	30	Surviving less than 24 hours	16	45
Measles	3	8	Surviving more than 24 hours	13	26
Guillain-Barré syndrome	1	400	Carbon monoxide poisoning	1	30
Mumps	1	9	(limited to patients who survived for an appreciable interval after the lethal exposure)		
Epidemic hepatitis	1	222	Emetine	1	70
Smallpox	32	581	Burns	11	45
Virus pneumonia	9	12			
Tuberculosis	3	48			
Boeck's sarcoid	11	5			
Coccidioidomycosis	2	9			
Blastomycosis	1	6			
Actinomycosis	1				
Torulosis	1				
			Total	1,402	

*The figures in the first column represent the number of times myocarditis was encountered. Wherever possible the number of cases of each disease, screened to ascertain the first figure, is given in column two. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

sarcoid, the current limitations of medical knowledge prevent proper cataloguing. A useful inclusive working classification, although one not free from the criticism of overlapping, is that proposed by Saphir.

MYOCARDITIS



A number of studies are contemplated to analyze the material at the Army Institute of Pathology, and will include the myocarditides associated with sulfonamide administration, acute infections of the upper respiratory tract, acute glomerulonephritis, acute meningococcemia, scarlet fever, diphtheria, spirochetal diseases, fungus diseases, certain parasitic diseases, rickettsial diseases, virus diseases, tuberculosis, Boeck's sarcoid, exfoliative dermatitis and septicemias, including subacute bacterial endocarditis.

It is perhaps worthy of note for its negative value only, that myocarditis was not encountered among eighty cases of typhoid fever, nor in thirty cases of bacillary dysentery. The former disease, particularly, has been classically associated with the production of Zenker's hyaline degeneration of skeletal muscle.

Although some of these myocarditides may be considered of academic rather than clinical interest, it is axiomatic that sound therapy can be based only on an accurate appraisal of the pathologic alterations. For example, myocarditis occurring with septicemia and subacute bacterial endocarditis, an academic problem prior to the adoption of sulfonamides and penicillin, is responsible for many of the fatalities in "bacteriologically cured" or arrested cases treated with these newer therapeutic agents.

REFERENCE

1. Saphir, O.: Myocarditis, A General Review With Analysis of 240 Cases, Arch. Path. 32: 1000, 1941, and 33:88, 1942.

MYOCARDITIS ASSOCIATED WITH ACUTE NASOPHARYNGITIS AND ACUTE TONSILLITIS

IRA GORE, LIEUTENANT COLONEL, MEDICAL CORPS, ARMY OF THE UNITED STATES, AND OTTO SAPHIR, M.D.,* RESIDENT CONSULTANT, ARMY INSTITUTE OF PATHOLOGY
WASHINGTON, D. C.

NONRHEUMATIC myocarditis occurring in the course of, or following acute infections of, the upper respiratory tract is a relatively unexplored subject. Rantz, Boisvert, and Spink,¹ who were associated with the Commission on Hemolytic Streptococcal Infections during World War II, set the incidence of this complication at 10.8 per cent. Their convincing epidemiologic and clinical studies did not include anatomic data. The series of eleven nonfatal cases of myocarditis following various infectious diseases reported by Candel and Wheelock² included one in which peritonsillar abscess was present. They also described one fatal case in which myocarditis was observed at post-mortem examination after acute tonsillitis. Scherf³ reported five nonfatal cases in which myocarditis followed acute tonsillitis, and stated that in his experience this complication occurred in 10 to 15 per cent of such cases. Substantial pathologic verification would be needed, however, before such high incidence could receive more than probational acceptance from the wary clinician (Saphir⁴).

In a study of the pertinent material available at the Army Institute of Pathology, thirty-five instances of nonrheumatic myocarditis were encountered in association with upper respiratory infections: acute tonsillitis in twelve† (Cases 1 through 12); and acute nasopharyngitis in twenty-three (Cases 13 through 35). In all cases the diagnosis of pharyngeal or tonsillar infection had been made clinically. Streptococci were cultured from the throat in twelve and from the heart's blood, post mortem, in three; grouping and subtyping had not been done. Septicemia was not considered of etiological moment since significant visceral alterations were absent in all thirty-five, and negative blood cultures were obtained in thirteen. *Corynebacterium diphtheriae* was absent from the culture material and diphtheria had been excluded clinically in each instance. The patients, with one exception (Case 35), were men; most of them were between 20 and 30 years of age, the youngest being 18 years and the oldest 43 years of age. More detailed information is available in Table I and in the appended clinical summaries.

Received for publication April 9, 1947.

*Pathologist, Michael Reese Hospital, Chicago, Ill.

†One of these twelve patients died of acute heart failure on the sixth day following tonsillectomy (Case 4).

TABLE I. CLINICAL AND ANATOMIC FEATURES OF MYOCARDITIS IN THIRTY-FIVE CASES OF ACUTE TONSILLITIS AND ACUTE NASOPHARYNGITIS

CASE NO.*	DURATION IN DAYS	CLINICAL MANIFESTATIONS OF HEART DISEASE PRESENT	STREPTOCOCCI IN THROAT CULTURE	BLOOD CULTURE	SULFA MEDICATION	BLOOD PRESSURE	TEMPERATURE/PULSE DISPROPORTION	BRONCHOPNEUMONIA	SEROUS EFFUSION	OTHER COMPLICATIONS
1	4	0	-	0	+	130/70	101°-80	0	-	-
2	4	+	+	0	0	104/60	98.8-110	0	-	-
3	5	0	+	0	+	130/80	103.2-88	0	-	-
4	5	+	+	0	+	85/70	102-130	+	-	Pericarditis
5	8	+	+	0	+	90/60	-	0	-	Anuria
6	10	+	+	0	+	85/60	-	0	+	Peritonissillar abscess
7	13	+	+	0	+	85/55	-	0	+	-
8	14	+	+	0	0	-	-	0	-	-
9	14	0	-	-	+	-	-	0	-	-
10	14	+	+	-	+	-	-	0	-	-
11	17	+	+	-	+	-	-	+	+	-
12	17	?	+	-	+	-	105 - 110	+	+	-
13	3	+	+	0	0	-	104.3-108	+	+	-
14	3	0	+	0	+	-	0	+	+	-
15	5	+	+	0	+	110/68	-	+	-	-
16	5	+	+	0	+	115/70	99.4-104	+	-	-
17	5	0	-	-	+	-	-	0	+	-
18	6	0	-	-	+	-	-	+	+	Anuria
19	6	+	+	-	+	-	101 - 86	0	+	-
20	7	0	+	0	+	-	-	+	+	-
21	7	0	+	+	+	94/64	105.2-108	+	+	-
22	7	+	+	-	+	-	102 - 140	+	+	-
23	8	+	+	-	+	-	-	+	+	Pulmonary infarction
24	8	+	-	0	+	130/76	-	+	+	-
25	8	+	-	0	0	120/80	98.6-168	+	+	-
26	9	+	-	0	0	84/70	-	+	+	-
27	11	?	+	+	+	-	-	+	+	-
28	14	+	-	-	+	122/74	-	+	+	-
29	16	0	-	-	+	98/42	101.4-130	0	-	-
30	17	+	-	-	+	50/50	105.4-158	0	-	Urachal sinus
31	19	+	-	-	+	118/60	-	+	-	-
32	23	0	+	+	+	106/70	103 - 90	+	-	Pericarditis
33	24	+	-	-	+	-	101.2-78	0	-	-
34	33	0	-	-	0	94/82	98.6-108	0	+	Visceral infarcts
35	38	+	-	0	0	-	-	0	-	-

*Cases 1 through 12 are acute tonsillitis, 13 through 35 are acute nasopharyngeal infections.

† Signifies an interstitial type of bronchopneumonia.

CLINICAL OBSERVATIONS

Elevation of temperature noted in thirty-three patients ranged between 99° and 104.4°F., averaging about 102°Fahrenheit. The pulse rate varied from 60 to 168 per minute. In fourteen the pulse rates and temperatures did not show proportionate variations; the pulse rate was disproportionately fast in six and disproportionately slow in eight. Cyanosis was noted in twelve patients, frequently in association with dyspnea which was observed in sixteen. Cheyne-Stokes respiration was present in two patients. Oppressive substernal pain was encountered in six, in every instance associated with dyspnea.

Electrocardiographic studies in five cases showed evidence of "myocardial damage" in three and disturbances in rhythm in two.

Hypotension occurred as a prominent clinical feature in five of twelve patients with nasopharyngitis in whom arterial blood pressures were recorded. There was low arterial tension in four of the seven patients with tonsillitis whose blood pressure readings were available. The values of these readings ranged from 98/42 to 85/55; there were five patients with systolic pressures of from 90 to 100 and four with pressures of from 80 to 90. A weak thready pulse, presumptive evidence of low blood tension, was observed in seven patients.

Twenty-six patients received sulfonamides; many were also given penicillin. Intravenous fluids were frequently administered, especially in the terminal phase of the illness. Azotemia as a result of urinary suppression developed in two of the patients who had received sulfonamides (Cases 6 and 19); their blood nonprotein nitrogen estimations were 85 and 210 mg. per cent, respectively.

The duration of hospitalization among the patients with nasopharyngitis averaged seven days, although five died within twenty-four hours (after illnesses which had begun from three to eight days before) and two survived for twenty-four days. Length of hospitalization among the patients with tonsillitis averaged eight and one-half days. The significant clinical manifestations of cardiac dysfunction are summarized in Table II; more detailed information may be obtained by referring to the appropriate case number in Table I and to the appended clinical summaries.

POST-MORTEM OBSERVATIONS

The cause of death was determined as cardiac failure in all cases. There were fifteen unexpected deaths, and in the remaining cases the pathologic findings included passive hyperemia of the viscera in all, pulmonary edema in most, and serous effusions in seventeen (ten of these were either extrathoracic or were unassociated with a pneumonic process).

In addition to cardiac changes, certain other abnormalities were noted at autopsy. Among the twenty-three patients with nasopharyngitis, ten had bronchopneumonia and three had interstitial pneumonia. Streptococci were cultured from the lungs of five and two of these, respectively. Thrombi were found in the left ventricle in one case in which there were also visceral infarcts and gangrene of the right leg. Pulmonary infarcts of unspecified origin were observed in another.

TABLE II. CLINICAL MANIFESTATIONS OF HEART DISEASE IN TWELVE CASES OF ACUTE TONSILLITIS AND TWENTY-THREE CASES OF ACUTE NASOPHARYNGITIS

	OCCURRED IN CASES	TOTAL NO. OF CASES
Cyanosis*	4, 5, 13, 16, 20, 23, 25, 26, 27, 29, 30, 35	12
Dyspnea* and/or orthopnea	4, 5, 15, 16, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 35	16
Cheyne-Stokes respiration	8, 21	2
Cardiac arrhythmia or irregularity	4, 5, 6, 10, 11, 13, 15, 22, 25, 26, 31	11
Disproportions of temperature and pulse	1, 2, 4, 5, 13, 14, 17, 20, 22, 23, 25, 30, 31, 33	14
Hypotension and/or weak thready pulse	6, 7, 8, 9, 11, 22, 25, 26, 30, 31, 35	11
Anginal pain	6, 9, 22, 25, 34, 35	6
Abnormal electrocardiogram	6, 10, 26, 33, 35	5
Unexpected death	1, 3, 9, 15, 16, 17, 18, 19, 20, 21, 22, 25, 29, 31, 34	15
Enlarged heart (x-ray)	19, 25, 30, 33, 35	5
Enlarged and tender liver	8, 25, 35	3
Pulmonary edema	14, 19, 23, 27, 32	5
Dependent edema	28, 35	2
Pulsus paradoxus	25	1

*A pneumonic process occurred in seven of the cases presenting cyanosis and in ten of the cases with dyspnea. Case numbers 1 through 12 represent acute tonsillar infection, numbers 13 through 35 refer to acute nasopharyngitis. In each case, reference to the appropriately numbered clinical summary will provide more detailed information.

Among the twelve cases of tonsillitis, bronchopneumonia and pericarditis occurred in one, bronchopneumonia with abscess formation in another, and peritonsillar abscess in a third. The parenchymatous organs in all 35 cases were the seat of varying degrees of cloudy swelling. There was moderate renal tubular damage and interstitial cellular infiltration in the two cases in which azotemia developed; sulfa crystals were identified in one of these. (See Table I and clinical summaries.)

Cardiac Findings.—At autopsy all but six of the hearts were found to be dilated; frequently they were increased in weight. Figures on the weights of organs were available in twenty-eight cases; the heart weighed 400 grams or more in thirteen (in three of these, 400 grams; between 400 and 499 grams in six; and between 500 and 560 grams in four). In the remaining cases one heart was regarded as "enlarged;" one, in a woman of average size, weighed 350 grams; two hearts were considered to be normal; three weighed less than 300 grams; and ten, between 300 and 400 grams. In the absence of hypertension or other possible causes for cardiac hypertrophy, the inflammatory process within the myocardium must have been largely responsible for the augmented weights.

Grossly, the hearts were usually described as soft, flabby, and friable. There was pallor of the myocardium which was gray or gray-streaked, or mottled with red or yellow, or both. Petechial hemorrhages were found subepicardially seven times and diffusely scattered throughout the myocardium three times. Mural ventricular thrombi were encountered in one case. Five of the hearts were regarded as grossly normal.

Histologically, the changes in the myocardium were striking. The lesions varied from circumscribed focal areas of inflammation, principally involving the interstitial tissues (Fig. 1), to areas of diffuse inflammatory infiltration associated with necrosis of muscle fibers (Fig. 2). Gradations from obviously very recent inflammation to definitely healing and organizing lesions were observed. The inflammatory process was patchy in distribution and there appeared to be no special region of the myocardium for which it had a predilection. When the heart was severely involved the intensity of the process frequently varied from one section to another. In instances of less intense involvement, it was not uncommon to find areas of the heart muscle in which inflammatory changes were minimal or even absent.

The inflammatory cellular response was predominately and characteristically mononuclear (Figs. 3 and 4). The proportion of each cell type encountered was not uniform and varied from one area to another. In the most cellular zones lymphocytes outnumbered the other elements, which included endothelial leucocytes and Aschoff cells,* mononuclear cells larger than lymphocytes with densely stained nuclei, and polymorphonuclear leucocytes. Occasionally, the last cell named made up as much as one-third of those present, but abscesses were not encountered. Polymorphonuclear leucocytes were less numerous in areas of less intense inflammation, and endothelial cells and Aschoff cells predominated in the areas where inflammation was least. These endothelial and Aschoff cells frequently formed small accumulations about a few intensely acidophilic, homogeneous muscle fibers, or somewhat more diffusely infiltrated the interstitial tissues, especially subendocardially about the orifices of the Thebesian vessels. The focal cellular accumulations around a few necrotic muscle fibers appeared to represent a very early and rapid morphologic change which we have designated as an "explosive lesion" (Figs. 5 and 6). Plasma cells and eosinophils were found in varying numbers. In older lesions fibroblasts were observed. Mast cells were present, as they are normally, but did not appear to participate to any extent in the inflammatory reaction. Bacteria were absent from all sections examined. Accompanying the inflammatory cells there was exudation of variable quantities of protein-rich fluid into the interstitial tissues.

The lesion involved both the scanty stroma within the muscle fasciculi and the more abundant stroma accompanying the blood vessels in the interfascicular septa. On this basis three histologic types of myocarditis could be distinguished. The first, which we have designated the *diffuse* variety, affected both

*Characterized by an abundant, faintly basophilic cytoplasm, a lightly stained oval nucleus, a thin sharp nuclear membrane, and a characteristic arrangement of the chromatin in the form of a central bar or node from which web-like processes extend toward the periphery; frequently called the "myocyte" following Anitschkow's original interpretation.

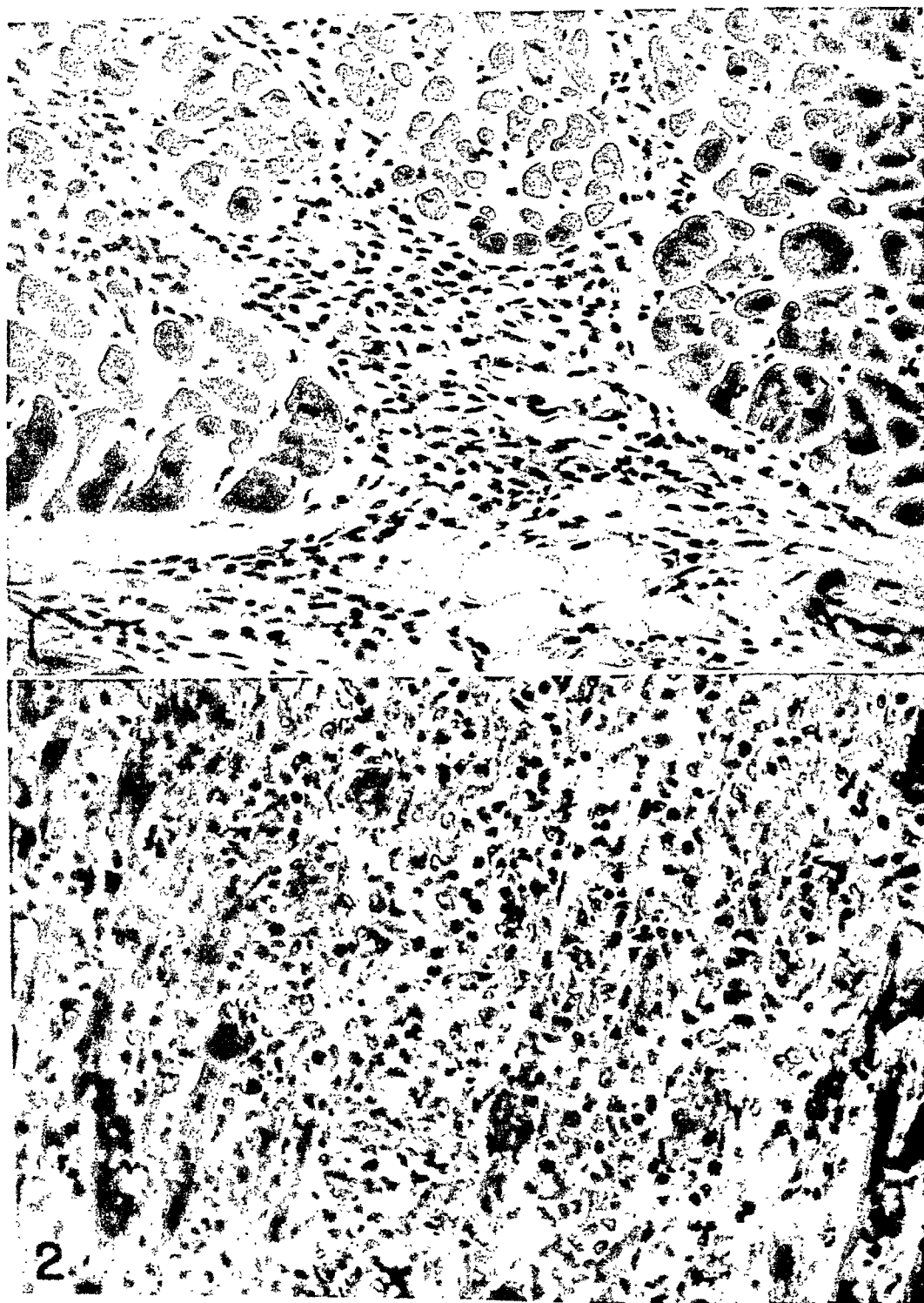


FIG. 1.—Case 3, AIP Accession 106073. Interstitial type of myocarditis. Note the predominantly mononuclear leucocyte infiltration of the stromal septa separating the muscle fasciculi. $\times 275$. Neg. 95854.

FIG. 2.—Case 34, AIP Accession 103357. Diffuse type of myocarditis. There has been rather extensive degeneration of the muscle fibers which are replaced by an intense, largely mononuclear, inflammatory infiltrate. Fibroblasts may also be identified in the lesion. $\times 310$. Neg. 95857.



Fig. 3.—Case 29, AIP Accession 89356. Accumulation of monocytes, Aschoff cells, and macrophages, replacing muscle fibers. $\times 600$. Neg. 95116.

Fig. 4.—Case 23, AIP Accession 165987. Early diffusely infiltrating myocarditis. Note shadows of muscle fibers in addition to the inflammatory cells. $\times 600$. Neg. 95113.

Fig. 5.—Case 23, AIP Accession 165987. Diffusely infiltrating myocarditis. Note the necrosis of muscle fibers. Round cells predominate. $\times 435$. Neg. 95125.

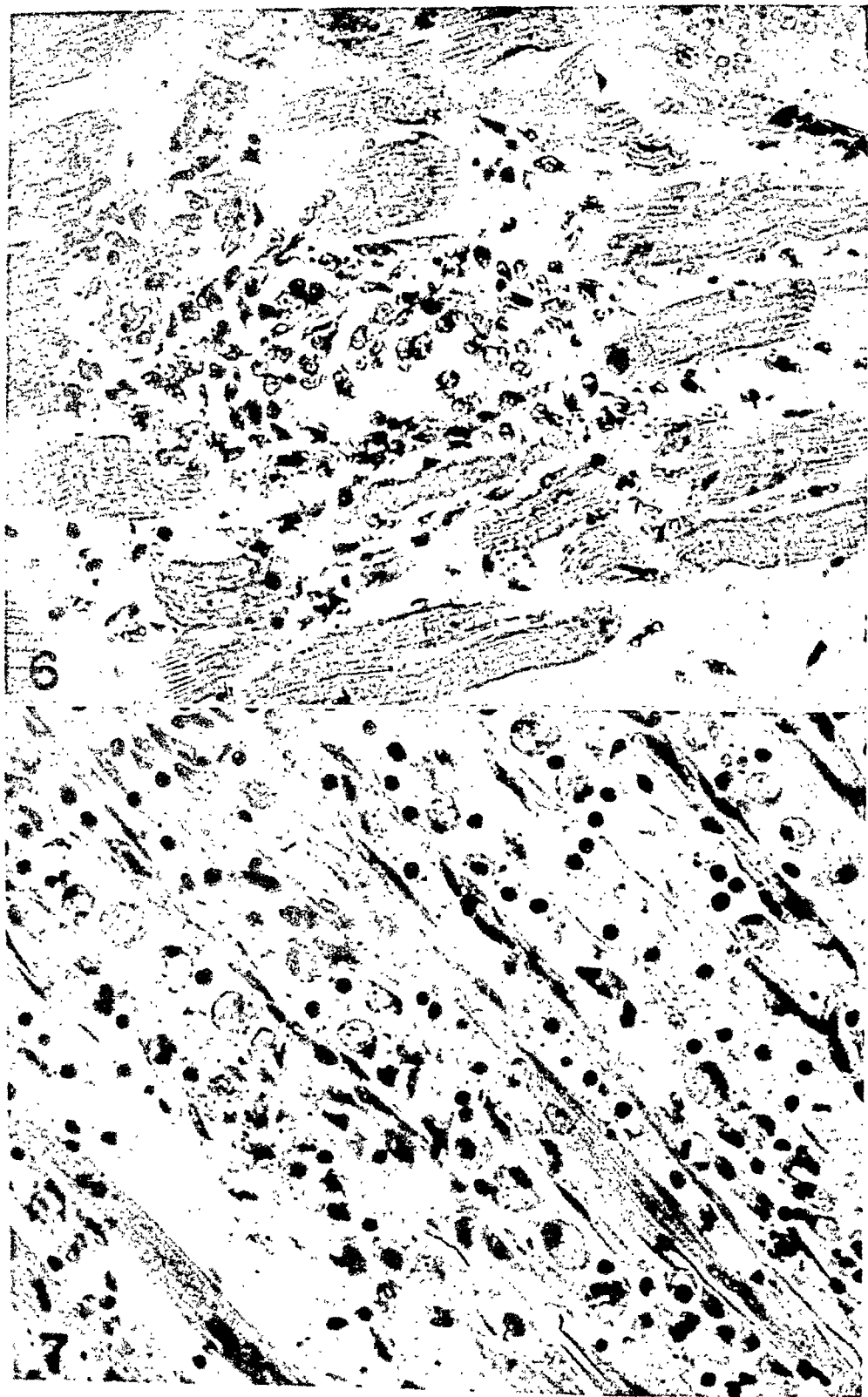


Fig. 6.—Case 31, AIP Accession 103378. Early "explosive" lesion showing an accumulation of endothelial leucocytes interrupting the course of a few heart muscle fibers. $\times 435$. Neg. 95114.

Fig. 7.—Case 22, AIP Accession 165985. Numbers of plump macrophages are present in the stroma, persisting after the disappearance of heart muscle fibers. $\times 435$. Neg. 95126.

the muscle and the stroma of the intrafascicular tissue and spilled over, to a variable extent, into the neighboring septa. It invariably was associated with necrosis of the cardiac musculature, which was of moderate degree or more in all except three of the nineteen cases of the diffuse type (Fig. 2). The second variety, the *interstitial* type, of which there were thirteen examples, was characterized by involvement of the interfascicular septal stroma in particular (Fig. 1). Muscle necrosis, which occurred in only three of this group was in each instance of mild degree and "explosive" type (Figs. 5 and 6). The last variant, which included three cases, was called the *mixed* type since it exhibited features of both of the others. In general, the estimated severity of the myocardial involvement was greatest in the diffuse histologic variety (see Table III). Both tonsillar and pharyngeal infections were represented in each type; however, the diffuse group included nine, the interstitial group two, and the mixed group one of the fatalities due to acute tonsillitis. In Table III the cases of each group are listed according to the severity of the myocarditis estimated in terms of plus signs as mild (1), moderate (2), and marked (3). It is evident from an inspection of this table that there is no correlation between the duration of the illness and the type or severity of the myocarditis. Fatalities occurred between 4 and 37 days, 7 and 24 days, and 3 and 23 days in each of the groups, respectively.

In the diffuse group where parenchymatous lesions were the rule, the state of disintegration, phagocytosis, and lysis of the necrotic muscle fibers served as a crude index of the duration of the disease (Figs. 7 and 8). Fibrosis, observed in eight cases and representing early healing, did not occur earlier than the thirteenth day. Considerable variation was observed, not only in the presence or absence of myocarditis in different areas of the myocardium but also in its severity and in its estimated duration. Hyalinized or granular necrotic muscle fibers with varying degrees of surrounding inflammation, occurring next to areas of almost complete myolysis, were suggestive of continued activity of the cardiopathic agent.

A similar patchy distribution of the cardiac lesion was observed in the interstitial variety of myocarditis. In that form there were no evident histologic criteria to indicate the duration of the process. Foci of collagenous necrosis were found in four instances of interstitial involvement and in one of the mixed group (Cases 3, 5, 29, 31, and 32) (Fig. 9). In the most striking of these was a prominent "palisade" reaction of large mononuclear (Aschoff) cells; however, the lesions did not have the perivascular position characteristic of the rheumatic nodule.

Increased weight of the heart in each of the three histologic variants appeared to be related to the intensity of the myocarditis. The respective incidence (expressed as the ratio of enlarged hearts to total number of hearts weighed) of augmented heart weight in the severe, moderate, and mild groups was 7:11, 5:15, and 2:5. In the group of "diffuse" parenchymatous lesions, naturally, the number of enlarged hearts was greatest, since a preponderance of the severe cases was in this group.

TABLE III. ANATOMIC AND HISTOLOGIC FEATURES OF MYOCARDITIS IN THIRTY-FIVE CASES OF ACUTE TONSILLITIS AND ACUTE NASOPHARYNGITIS

	DIFFUSE																				MIXED	INTERSTITIAL														
	2	17	1	6	9	10	12	15	16	7	8	11	14	23	25	26	30	34	35	20		3	33	18	19	21	29	4	13	22	24	27	28	31	32	5
Case number																																				
Severity*	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	2	2	3	1	1	1	1	2	2	2	2	2	2	2	2	2	3
Duration in days	4	5	4	10	14	14	17	5	5	13	14	17	3	8	8	9	17	33	38	7	5	24	6	6	7	16	5	3	7	8	11	14	19	23	8	
Heart weight in grams	298	350	425	-	'N'	400	315	250	430	355	560	520	380	375	Enl	460	-	430	Enl	450	387	375	400	406	318	390	N	260	400	-	365	-	340	330	500	
Cardiac dilation	-	+	+	+	+	0	+	+	+	-	+	+	+	+	+	0	0	+	+	+	+	+	0	+	+	+	0	+	+	+	+	+	+	+	+	
Gross alterations of myocardium	+	+	+	+	+	0	-	0	+	0	-	+	+	-	+	+	0	+	+	+	+	+	0	0	-	0	0	-	+	0	+	+	+	+	0	0
Diffuse involvement*	1	2	1	2	2	2	1	2	2	1	3	1	3	3	2	3	3	3	3	1	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Muscle necrosis*	1	1†	1†	2	2	2	2	2	2	3	3	3	2†	3	3	3†	3	3	3	1	2†	3	0	0	0	0	0	0	1†	0	0	0	0	0	1†	1†
Interstitial involvement*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	1	1	1	1	2	2	2	2	2	2	2	2	3	
Fibrosis	0	0	0	0	0	F	F	0	0	F	0	F	0	0	0	0	F	F	F	0	0	F	0	0	0	0	0	0	0	0	0	0	0	0	0	

- Indicates lack of descriptive statement in the available records.

* Estimated as mild (1), moderate (2), and marked (3).

N Under heart weight represents normal.

† Listed with muscle necrosis indicates an "explosive" type of lesion.

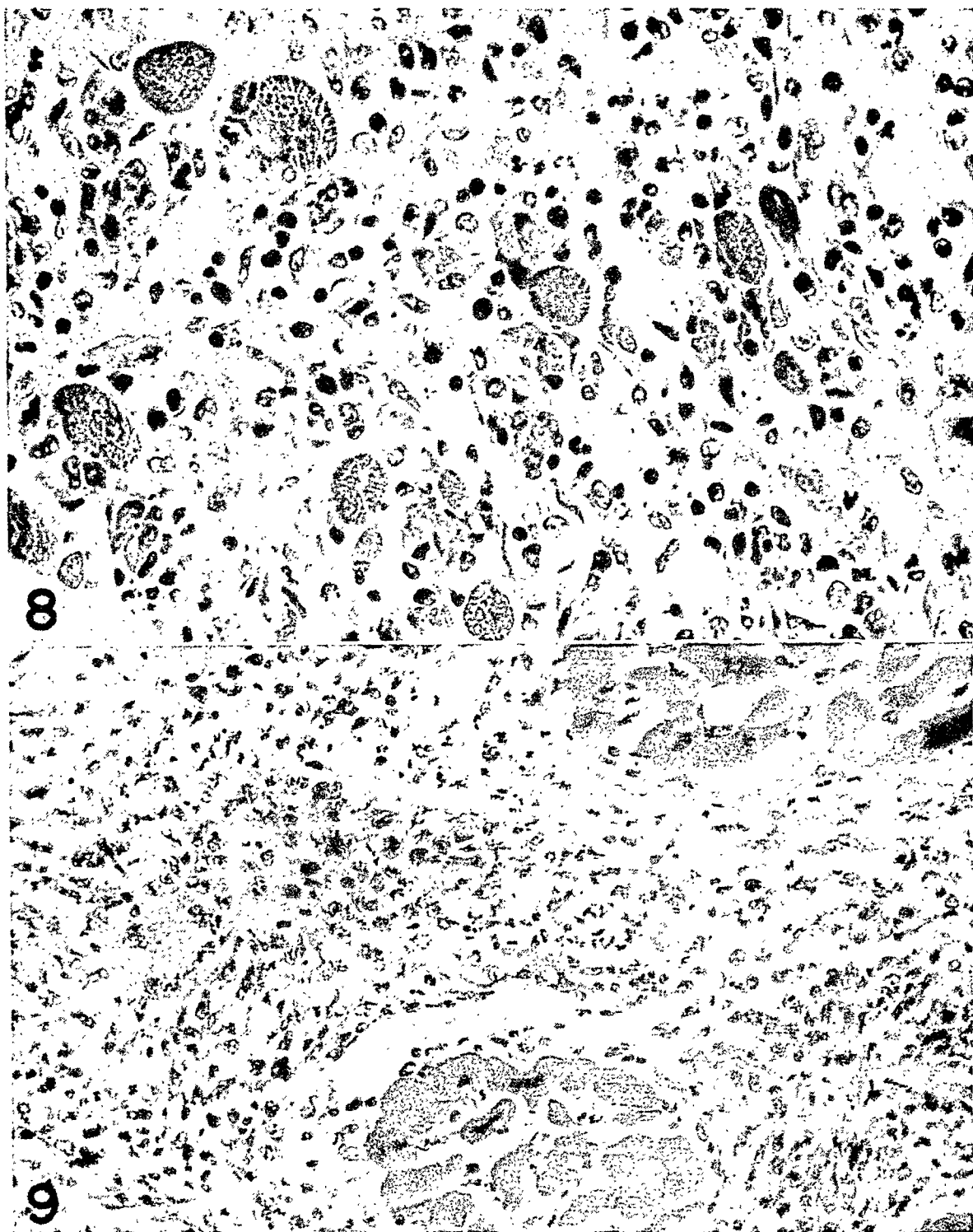


Fig. 8.—Case 34, AIP Accession 103357. Diffuse type of myocarditis. Lymphocytes, endothelial leucocytes, and a few polymorphonuclear leucocytes make up the inflammatory infiltrate. $\times 455$. Neg. 95131.

Fig. 9.—Case 5, AIP Accession 139424. Two foci of "fibrinoid" necrosis of connective tissue occasionally found in the interstitial type of myocarditis. The palisaded cells are identical with those that contribute to the formation of the Aschoff nodule. Points which differentiate it from the latter are the lack of the characteristic perivascular position and the absence of giant cells. The cardiac valves, endocardium, and pericardium were intact. $\times 275$. Neg. 95852.

The various clinical manifestations of heart disease and the frequency with which they occur in each of the three histologic variants are presented in Table IV. Although the figures are too small to be statistically conclusive, they suggest that hypotension and anginal pain are more frequent in the diffuse type of myocarditis. This again may merely be a reflection of the preponderance of severe myocarditis in that group.

TABLE IV. OCCURRENCE OF CARDIAC SYMPTOMATOLOGY IN THREE HISTOLOGIC TYPES OF MYOCARDITIS ASSOCIATED WITH ACUTE TONSILLAR AND ACUTE NASOPHARYNGEAL INFECTIONS

	DIFFUSE MYOCARDIAL LESION (19 CASES)	INTERSTITIAL MYOCARDIAL LESION (13 CASES)	MIXED TYPE OF MYOCARDIAL LESION (3 CASES)
Cyanosis	6	5	1
Dyspnea and/or orthopnea	7	7	2
Cheyne-Stokes respiration	1	1	0
Cardiac arrhythmia or irregularity	6	4	1
Disproportions of temperature and pulse	7	5	2
Hypotension and/or weak thready pulse	9	2	0
Anginal pain	5	1	0
Abnormal electrocardiogram	4	0	1
Unexpected death	7	6	2
Enlarged heart (x-ray)	3	1	1
Enlarged and tender liver	3	0	0
Pulmonary edema (terminal)	2	3	0
Dependent edema	1	1	1
Pulsus paradoxus	1	0	0

DISCUSSION

The clinical relationship between acute nasopharyngeal or tonsillar infections and subsequent acute rheumatic fever is well recognized. Little is known about any other cardiac complications. Lulled by the almost axiomatic teaching (which should be discarded) that "myocarditis other than that associated with acute rheumatic fever and diphtheria is for practical purposes nonexistent," the clinician has been almost oblivious to many inflammatory conditions of the myocardium. Seventy-five per cent of the cases of myocarditis in a series of 1,402 collected at the Army Institute of Pathology were nonrheumatic and nondiphtheritic. It has become increasingly evident with the more common use of the electrocardiogram that reversible, fleeting, or transitory alterations may occur during or shortly after a number of infectious diseases. The interpretation of the significance of such changes is considerably varied since a pathologic foundation is lacking. Estimates of incidence (cited in the introductory paragraphs) of cardiac involvement following the common cold and acute tonsillitis are in large part based on electrocardiographic studies.

Why should there be such a dearth of anatomic data in so prevalent a disease? First, and most fortunately for humanity, the death rate is undoubtedly very low, although further studies are necessary to establish the figure. A second reason is derived from the first: because death is not common and because central

laboratories of pathology are so few, it is rare for any one individual to have the opportunity to see more than occasional sporadic fatal cases. Following the too common practice, myocarditis has been considered idiopathic when rheumatic fever and diphtheria were ruled out, and, in the absence of a sufficient number of cases, correlation with a disease generally considered to be innocuous has been regarded as unreasonable. A third reason is, that because of the patchy distribution of the inflammatory process throughout the heart muscle, myocarditis has undoubtedly often been overlooked. The few blocks of myocardium routinely examined constitute but the crudest form of sampling; there can be no doubt that more thorough histologic examination of the heart would have uncovered a significantly greater number of lesions. Until the correlation with the antecedent infection is firmly established and a proper index of suspicion created, the clinician will continue to overlook many cases of myocarditis. As a matter of fact, the carditis was recognized clinically in only three of the cases forming the basis of this report (Cases 25, 33, and 35).

It is possible only to conjecture concerning etiology. The bacteriologic data available, which incidentally coincide with those generally accepted for acute tonsillar and nasopharyngeal infection, are sufficient only to cast the shadow of suspicion on the streptococcus as the etiological agent. The usual presence of this organism in the normal oral flora makes it difficult to evaluate its significance when isolated. Here is obviously a fruitful field for further bacteriologic study, using the streptococcal grouping and typing techniques developed by Lancefield.⁵ The role, if any, played by the unidentified virus or viruses considered the primary etiological agent of the common cold is unknown. Nevertheless, controlled experimental infections of laboratory animals with the known viruses of respiratory infections have not produced myocardial lesions (Smadel⁶). Sulfonamides administered to twenty-six of the patients did not cause or appreciably contribute to myocarditis in this series, since the pathologic changes were the same as those in the hearts of patients who had no such medication. Furthermore, periarteritic and arteritic lesions of the type reported by Rich⁷ and demonstrated by French^{8,9} in the heart in sulfonamide hypersensitivity were absent from the cases reported here, as were also the visceral cellular infiltrates rich in acidophilic histiocytes and leucocytes. (Renal suppression in two patients resulted from the summated effects of circulatory failure and sulfonamides.)

Naturally, a full account of the pathogenesis is dependent on determination of etiology. But there are important implications in certain of our observations: absence of histologically demonstrable organisms in the myocardial lesions (Schenken and Heibner¹⁰ have reported the cultural isolation of a streptococcus from the myocardium of a case of "isolated" myocarditis); predominance of mononuclear cells in the inflammatory response; and frequency of parenchymatous necrosis somewhat similar to that produced by diphtheria toxin. Although septicemia was ruled out, the possibility of transitory bacterial seeding must be taken into consideration; however, if such an event took place, organisms must have been destroyed rapidly. Our material does not permit us to comment

regarding the role of hypersensitivity, but the clinical data of Rantz, Boisvert, and Spink¹ indicate a striking relation between the frequency of recurrences of acute upper respiratory infections and the incidence of myocardial involvement.

Since myocarditis associated with these infections has been largely unrecognized to date, we do not consider it amiss to comment on the problems of prognosis and of therapy. In general, the prognosis should be viewed with a certain degree of optimism. Although there is good reason to suspect a high morbidity from this disease, the scarcity of pathologic data testifies to the low mortality rate. Even in the fatal cases, a striking tendency toward spontaneous cure is suggested by the presence of fibrosis as seen in a significant proportion of the hearts examined in this study.

The most rewarding field lies in the treatment of patients whose hearts have sustained an intermediate degree of damage. Complete rest diminishes the physiologic demands upon the heart. Certain of the cardiac stimulants, by increasing the efficiency of that portion of the myocardium which still retains functional capacity, may prolong survival to the point where the physiologic healing mechanisms have had a chance to cope with the inflammatory process.

Data in the clinical records of the cases we have studied make it clear that great care must be exercised in giving fluid intravenously. Intravenous administration of fluids, which at present is a routine and valuable procedure in the treatment of "common" shock where the heart is normal, may fatally overload a diseased heart which has become incapable of sustaining even normal blood tension. An increasing awareness on the part of the physician of the cardiac effects, not only of tonsillitis and nasopharyngitis but also of many other infectious diseases and processes, would lead to more frequent differentiation of cardiacgenic shock for which intravenous fluids may be lethal from the more common variety of shock for which intravenous fluids may be lifesaving.

In reviewing these cases and others of postinfectious myocarditis, it becomes apparent that there is a feature of the disease which hinders clinicians and pathologists from associating the development of cardiac manifestations with the infectious process responsible for them. Heart symptoms often become evident at a time when the clinician and the patient have concluded that the primary disease process is under control, with the result that developments are frequently regarded as an independent process. Certain cases reported in the literature (erroneously, we believe) as Fiedler's or "isolated" myocarditis illustrate such a mistake. Frequently, the primary disease is considered innocuous just as is the common cold or acute nasopharyngitis. Nevertheless, in spite of a clinically "free" interval in such cases, the pathologic findings are in no way different from those without such an interval. A well-established clinical analogy exists in diphtheritic infections where it is recognized that myocarditis may develop after the demonstrable local inflammatory process has largely subsided. (See Cases 3, 6, 8, 9, 10, 11, 15, 21, 31, and 33.)

SUMMARY

Thirty-five instances of fatal myocarditis attributable to acute nasopharyngeal and tonsillar infections have been reported. The available evidence indicates that these are samples of a not uncommon type of cardiac disease which fortunately has a relatively good prognosis. Further investigation should be carried on to establish fully the etiological agent and the pathogenesis of the lesion. Although the pathologic observations indicated that all patients died of cardiac failure, heart disease was suspected clinically in only three, and in fifteen patients death was unexpected. Significant clinical observations which would seem to be of importance in the recognition of the process were: disproportion of the temperature and pulse rate, hypotension, thready or feeble pulse, and substernal oppression. Cyanosis, dyspnea, and orthopnea occurred frequently.

Autopsy findings included significant enlargement of the heart in many cases. The microscopic changes, similar in both nasopharyngeal and tonsillar infections, have been classified in three overlapping groups. In all of these the inflammatory process was observed to be patchy, frequently showing considerable variation in intensity from one area to another and having no predilection for a particular portion of the myocardium. Significant (moderate or marked) degrees of muscle degeneration observed in the diffuse type of myocardial lesion were not present in the interstitial form. The cellular reaction, which was characteristically more intense than that observed in diphtheritic myocarditis, was predominantly mononuclear, but significant numbers of polymorphonuclear leucocytes accumulated at sites of more severe inflammation.

Although the figures are too small to justify conclusions, there appears to be significant correlation between the clinical occurrence of hypotension and the estimated severity of the myocarditis, since it was a feature in every severe case in which the blood pressure was recorded. The only available electrocardiograms (four), abnormal in every case, were from patients whose hearts showed muscle degeneration of moderate or marked degree. Anginal pains were related to the presence of hypotension. Fibrosis of the heart muscle was related both to the muscle degeneration and to duration of illness.

In therapy, attention is called to the danger involved in the administration of intravenous fluids.

CLINICAL ABSTRACTS

Tonsillitis (Cases 1-12).—

CASE 1.—A.I.P. Accession 140817. A 37-year-old white man contracted acute tonsillitis while undergoing topical penicillin treatment for gingivitis. Sulfadiazine therapy was instituted but was discontinued on the third day, though the throat infection was still present. The temperature was 101°F.; pulse rate, 80; respirations, 20; and blood pressure 130/70. He was found dead in bed on the fourth hospital day.

CASE 2.—A.I.P. Accession 113630. A 24-year-old Negro man, admitted with complaints referable to hemorrhoids, was found to have mild acute tonsillitis. Temperature was 98.8°F.; pulse rate, 110; respirations, 24; and blood pressure, 104/60. Urinalysis and Wassermann reaction were negative; the white blood cell count was 7,000. Throat culture revealed streptococci and staphylococci. Weakness was a prominent clinical feature. The temperature on the

second day was 99°F., but both temperature and pulse rate rose on the third day. Blood culture was negative, white blood cells numbered 12,000, with 68 per cent polymorphonuclear cells. Roentgenograms on that day showed a slight increase of the hilar and peribronchial markings. Death occurred seventy-eight hours after admission to the hospital.

CASE 3.—A.I.P. Accession 106073. A 24-year-old white man was admitted to the hospital with moderate tonsillitis of two days' duration. The temperature was 101°F., the heart and lungs were clear. Sulfathiazole therapy was started on the first hospital day when the temperature was 102° Fahrenheit. The temperature dropped to 99°F., the tonsillitis appeared to be subsiding, and the patient appeared comfortable. The following morning he was found dead in bed. Throat culture revealed hemolytic streptococci.

CASE 4.—A.I.P. Accession 102488. A 25-year-old white man had had acute tonsillitis four months previously. On admission to the hospital his temperature was 97°F.; pulse rate, 80; respirations, 20; blood pressure, 130/80; and white blood cells, 9,600. Hypertrophic tonsils were removed under local anesthesia. On the second postoperative day there was considerable pain locally, the temperature was 99.6°F., and pulse rate was 74. Swelling of the neck and hemorrhage from the site of operation appeared on the third day as the temperature rose to 103.2°F., and the pulse rate to 88. Sulfadiazine was given. Cyanosis, dyspnea, restlessness, and irregularity of pulse developed the following day. Oxygen and tracheotomy provided no relief. White blood cells numbered 15,500, with 83 per cent polymorphonuclear leucocytes; blood culture was negative. Sulfathiazole was given intravenously, but there was no apparent response. On the fifth day the temperature was 102.8°F.; the pulse rate, 126; and the blood pressure, 145/90. Death occurred early the next morning.

CASE 5.—A.I.P. Accession 139424. An 18-year-old white man was admitted to the hospital with acute tonsillitis of one day's duration. His temperature was 99.8° Fahrenheit. Sulfadiazine was administered. When the temperature rose the following day to 104°F., sulfadiazine was augmented by penicillin. White blood cells numbered 27,000, with 90 per cent polymorphonuclear leucocytes. On the fourth day the temperature was 101°F. to 102°F., and white blood cells numbered 12,600. Throat culture yielded alpha streptococcus, *Staphylococcus albus*, and hemophilus. On the sixth day with the condition of the pharynx unchanged, there was x-ray and clinical evidence of bronchopneumonia. Temperature was 102°F., white blood cells numbered 9,000, with 88 per cent polymorphonuclear leucocytes. Cyanosis, dyspnea, and auricular fibrillation became evident. On the seventh day pulmonary edema developed and the patient died. The last recorded temperature was 102°F., with a pulse rate of 130 per minute.

CASE 6.—A.I.P. Accession 140417. A 31-year-old white man was hospitalized for acute tonsillitis and treated with sulfadiazine. On the second day the temperature was 99.6°F.; white blood cells, 23,000, with 90 per cent polymorphonuclear leucocytes. There was still a mild leucocytosis on the fifth day, the white blood cells being 12,600. The local process had largely resolved by the ninth day, when he complained of sudden pain. The heart sounds were rather poor, rhythm irregular, blood pressure 85/70, and radial pulse weak. The following day these manifestations persisted. The patient's color was ashen, respirations labored, temperature 101°F., and blood pressure was 70/?. Pulmonary edema was present. An electrocardiogram demonstrated ventricular tachycardia. Anuria noted on the last day of life was attributed to shock. Blood nonprotein nitrogen was 210 mg. per cent and the blood sulfa level was 1.6 milligrams. Post-mortem blood culture was negative.

CASE 7.—A.I.P. Accession 146376. A 25-year-old white man had received sulfathiazole for nine days in treatment of tonsillitis. At that time the white blood cells numbered 4,300. On the eleventh day, a peritonsillar abscess developed. Throat culture was reported as negative for diphtheria. Heart sounds were faint with a reduplication of the first sound, the pulse of poor quality, blood pressure, 90/60, white blood cell count, 21,500, and sedimentation rate accelerated. There was no elevation of temperature. Death from circulatory failure occurred after a period of Cheyne-Stokes respirations and convulsions.

CASE 8.—A.I.P. Accession 164750. A 23-year-old white man was hospitalized on the third day of acute tonsillitis. Throat smear and culture were negative for diphtheria. Blood count showed a moderate leucocytosis with a "left shift" in the Schilling index. Treatment, which included penicillin and sulfadiazine, was stopped when the fever subsided, but leucocytosis of 14,000 remained. On the twelfth day of illness the liver was observed to be swollen and tender. The patient was cyanotic, heart sounds were distant, and blood tension low, 85/60. Death occurred two days later, following convulsions and Cheyne-Stokes respirations.

CASE 9.—A.I.P. Accession 125363. A 33-year-old German had acute rhinitis, acute maxillary sinusitis, and acute cellulitis of the face subsequent to tonsillitis. Temperature was elevated. Two blood cultures were sterile. Sulfadiazine and penicillin appeared to control the infection effectively so that the clinical status was described as good. On the fourteenth day the patient suddenly complained of chest pain. The heart sounds were poor, pulse thready, and arterial tension was 85/55. Death occurred in a short time.

CASE 10.—A.I.P. Accession 133950. A 24-year-old white man was admitted to the hospital with an acute peritonsillar infection from which hemolytic streptococci were cultured. White blood cells numbered 22,400, with 89 per cent polymorphonuclear leucocytes. Sulfadiazine was administered and the temperature which had been high reverted to normal by the fourth day. On the ninth day, during seeming convalescence, bradycardia and acute heart failure developed. Cyanosis and mild convulsive episodes followed. Leucocytes numbered 17,500, with 82 per cent polymorphonuclear cells. Throat smear and culture were negative for diphtheria. The blood nonprotein nitrogen was 115 and rose to 192 mg. per cent. Erythrocyte sedimentation rate was normal. Electrocardiograms showed daily variations, including auricular fibrillation and idioventricular rhythm. Death occurred on the fourteenth day.

CASE 11.—A.I.P. Accession 145824. A 21-year-old white man was admitted to the hospital with acute tonsillitis of one day's duration. The temperature was 104.8°F., the white blood cells numbered 11,800. Throat culture was negative for diphtheria. Sulfadiazine therapy was started on admission and was augmented by penicillin on the third day because tonsillitis persisted despite subsidence of the fever. Chemotherapy was stopped on the ninth day when the condition of the tonsils was improved, although they were still inflamed. Convalescence seemed uneventful until the sixteenth day when abdominal pain and vomiting started. Despite antishock measures to combat a weak thready pulse, poor heart sounds, and gallop rhythm, death occurred on the seventeenth day. The leucocyte count on the day of death was 15,500.

CASE 12.—A.I.P. Accession 104420. A 19-year-old white man was admitted to the hospital with acute tonsillitis of one week's duration. The leucocyte count was 19,800, with 85 per cent polymorphonuclear cells. Despite sulfonamide therapy, leucocytosis was progressive. It was 33,000 on the sixteenth day when evidence of bronchopneumonia was noted. Death occurred on the following day.

Acute Nasopharyngitis (Cases 13-35):—

CASE 13.—A.I.P. Accession 143838. An 18-year-old white man was hospitalized with acute nasopharyngitis and laryngitis of two days' duration. Overnight the temperature rose rapidly from 99.8° to 105° Fahrenheit. The pulse rate with that temperature was 110; the patient appeared extremely toxic and there was slight cyanosis. An early pneumonic process was present at the base of the right lung. Despite penicillin therapy, oxygen, and intravenous fluids, there was progressively increasing cyanosis; the pulse rate rose to 140 per minute and death occurred on the third day of illness, twenty-four hours after admission. Streptococci were cultured from the lungs and bronchi post mortem.

CASE 14.—A.I.P. Accession 89894. A 26-year-old white man was acutely ill with severe nasopharyngitis: temperature was 104.3°F.; pulse rate, 108; and respirations, 22 per minute. The white blood cell count, which was 23,000 the day following admission, fell to 13,300 on the second hospital day. Sulfadiazine therapy had to be discontinued because of an undue emetic effect. On the third day pulmonary edema developed and the patient died. A post-mortem culture of the heart blood was sterile.

CASE 15.—A.I.P. Accession 96506. An 18-year-old white man was hospitalized with an acute respiratory infection of thirty-six hours' duration. The temperature was 104°F.; pulse rate, 120; and respirations, 22 per minute. Under sulfathiazole therapy the temperature dropped overnight to 100.2° Fahrenheit. The pulse rate was 112; the white blood count 20,000. On the second day, improvement appeared progressive; temperature dropped to 99.4°F. and pulse rate to 90 per minute. Late that day, however, the patient became dyspneic, the pulse rate rose to 132, and death occurred suddenly in the early hours of the following morning. Hemolytic streptococci were cultured from the lungs post mortem.

CASE 16.—A.I.P. Accession 150897. A 33-year-old white man was hospitalized with an acute upper respiratory infection of one day's duration. The temperature was 102.4°F.; pulse rate, 100; and respirations, 20 per minute. The white blood count on the first hospital day was 18,000, and roentgenograms showed a small pneumonic patch at the base of the right lung; the temperature was 104.2°F., and blood pressure was 11/68. Despite sulphadiazine therapy, the pneumonic process extended, and on the third day the temperature was 104°F. and the pulse rate 120 per minute. Dyspnea and cyanosis were noted on the morning of the fourth day when the patient died. Penicillin was administered terminally. Streptococci had been isolated from the sputum and were also cultured from the lungs post mortem.

CASE 17.—A.I.P. Accession 114683. A 20-year-old white man was admitted to the hospital with a "cold" of two days' duration. Two and one-half months previously he had had a type I pneumococcal pneumonia which had responded well to sulfadiazine therapy and was without evident residua. Temperature was 99.4°F. and pulse rate 104 per minute. The temperature was 99°F. the next morning. The patient died suddenly sixty-five hours after admission.

CASE 18.—A.I.P. Accession 94336. A 40-year-old white man was hospitalized with an acute "upper respiratory infection" of six days' duration. The temperature was 102.4°F.; pulse rate, 96; and blood pressure, 115/70. Physical signs and roentgenograms indicated a pneumonic involvement of the bases of both lungs. The white blood cell count was 11,100. The pneumonic process had spread by the second day, when acute heart failure developed suddenly and the patient died. Therapy had included sulfadiazine.

CASE 19.—A.I.P. Accession 114270. A 38-year-old Negro was acutely ill with a three-day history of cough, chills, and fever. The admission temperature was 102.4°F.; pulse rate, 108 per minute; and white blood cell count, 30,500. Sulfadiazine was administered, but was discontinued and penicillin substituted when oliguria was observed on the first hospital day. Roentgenograms taken on admission disclosed pulmonary congestion and an enlarged heart. Death occurred on the third day when pulmonary edema suddenly developed.

CASE 20.—A.I.P. Accession 86952. A 24-year-old white man had a cough and sore throat of one week's duration. The temperature was 101°F. and the pulse rate 86 per minute. Three and one-half hours after admission the patient became restless, dyspneic, and cyanotic; coma developed, and death supervened within one-half hour.

CASE 21.—A.I.P. Accession 98439. A 19-year-old white man was hospitalized on the second day of an illness diagnosed as acute nasopharyngitis. The temperature was 104°F. and the pulse rate 120 per minute. Sulfadiazine therapy was instituted. After apparent clinical improvement, a pneumonic process, confirmed by x-ray, developed on the sixth day. The patient went into Cheyne-Stokes respiration and died the same day. At autopsy, pneumococcus, type XVII, was isolated from the heart blood; and identical organisms, as well as streptococci, were cultured from the lungs.

CASE 22.—A.I.P. Accession 135455. A 25-year-old white man was admitted to the hospital with "substernal oppression" which had developed on the fourth day of a "cold." Temperature was 99°F.; pulse rate, 84; and respirations, 18 per minute. Blood pressure was 94/64. The white blood cell count was 10,800 and the sedimentation rate was accelerated. Heart sounds were weak. Substernal pain and cough persisted and the following day the temperature was 105.2°F.; the

pulse rate, 108 per minute; and the respiratory rate was increased to 32. The lungs were clear to physical examination; a blood culture was sterile. Sulfathiazole therapy was instituted. Cardiac irregularity, consisting of extra systoles and paroxysmal fibrillation, was noted. Death occurred suddenly on the second hospital day, the seventh day of illness.

CASE 23.—A.I.P. Accession 165987. A 30-year-old white man was hospitalized on the seventh day of an acute infection of the upper respiratory tract. The temperature was 102°F. and the pulse rate was 140 per minute. There was moderate dyspnea and cyanosis and evidence of consolidation at the bases of both lungs. Penicillin and sulfadiazine were without evident effect. On the day following admission cyanosis and dyspnea were more marked, the pulse was weak and thready, and the patient died with pulmonary edema. Streptococci were cultured from the lungs, post mortem.

CASE 24.—A.I.P. Accession 76869. Early in the course of a mild "cold," a 25-year-old Negro had sudden pleuritic chest pain accompanied by hemoptysis. On admission to the hospital the temperature was 99.4°F.; pulse rate, 86; and respirations, 24 per minute. Blood pressure was 130/76. White blood cell count was 16,100. Sulfathiazole was administered when roentgenograms of the chest revealed irregular mottling in both lower lobes. During the succeeding days the pulmonary process spread and fluid accumulated in the left chest. There was progressive dyspnea, and death occurred with pulmonary edema on the eighth day of illness.

CASE 25.—A.I.P. Accession 139665. A 35-year-old white man noted orthopnea early in the course of a mild "upper respiratory infection." He was hospitalized on the fourth day because of "substernal pressure." The heart was enlarged. On the fifth day the pulse was found to be of poor volume, very irregular, and very rapid (168 per minute). Blood pressure was difficult to ascertain because of a pulsus paradoxus, but was recorded at 120/80. The veins of the neck were distended; the liver was tender. Temperature at this time was 98.6°Fahrenheit. Digitalis was prescribed. On the sixth day there was a slight pulse deficit (120 apical rate, 104 pulse rate) and the blood pressure was 110/86. Death occurred suddenly on the eighth day of illness. A culture of the heart blood, post mortem, was sterile.

CASE 26.—A.I.P. Accession 111927. A 32-year-old white man was admitted to the hospital on the fifth day of a "common cold." The temperature, which was 102.6°F. on admission, rose to 104.4°F. within a few hours. Pulmonary signs developed on the first hospital day. The white blood cell count was 7,100. Roentgenograms on the following day showed "either a central pneumonitis or congestive heart failure." The temperature was now 104°F.; the white blood count, 11,700. On the third hospital day (the eighth day of illness) there was cyanosis and dyspnea; the pulse was weak and rapid, the blood pressure was 84/70, and a gallop rhythm was present. An electrocardiogram demonstrated myocardial damage. The course was rapidly downhill and death occurred early in the morning of the ninth day. Blood cultures taken on the second and third hospital days were sterile.

CASE 27.—A.I.P. Accession 109627. A 25-year-old white man was admitted to the hospital with a rash and fever of five days' duration. A diagnosis of measles was made. The rash faded and the temperature subsided to normal by the second hospital day. On the third day, the temperature had risen again to 102°F. and a diagnosis of acute nasopharyngitis was made. On the fifth day, sulfadiazine was administered because of pleuritic chest pain. Pulmonary involvement was demonstrable in roentgenograms; the white blood cell count was 15,400; and hemolytic streptococcus was cultured from the sputum. There was progressive cyanosis and dyspnea, and death occurred following the development of pulmonary edema. At autopsy both heart blood and lung cultures were positive for the same streptococcal organism (Group A, type III).

CASE 28.—A.I.P. Accession 141224. A 20-year-old white man was admitted to the hospital with chest pain and dyspnea which had developed on the tenth day of acute nasopharyngitis. Dyspnea seemed far out of proportion to the signs of involvement of the chest. X-ray revealed "soft infiltration in the hilar regions." Therapy, which was without beneficial effect, included sulfadiazine and penicillin. The white blood cell count on the second hospital day was 6,300.

On the third day 600 c.c. of blood-tinged pleural fluid was removed from the chest but reaccumulated rapidly. There was marked ankle edema at the time of the patient's death on the fourth hospital day, the fourteenth day of illness.

CASE 29.—A.I.P. Accession 89356. A 43-year-old white man was admitted to the hospital after an acute "upper respiratory infection" of five days' duration. The temperature was 103.6°F.; pulse rate, 110; and respiration, 22 per minute. Blood pressure was 122/74. Sulfadiazine was prescribed. The white blood count was 7,400 and there was no clinical evidence of pulmonary disease on the third hospital day, although the temperature was still elevated. The white blood cell count on the tenth day of illness (fifth hospital day) was 6,000, the polymorphonuclear leucocytes showed a marked "left shift." Death occurred unexpectedly on the sixth hospital day, the eleventh day of illness, when restlessness, cyanosis, and dyspnea suddenly appeared.

CASE 30.—A.I.P. Accession 73793. An 18-year-old white man was admitted to the hospital on the twelfth day of an acute "upper respiratory infection." The temperature was 101.4°F.; the pulse, 130; and the blood pressure, 98/42. Roentgenograms of the chest showed essentially no pulmonary disease but did demonstrate cardiac enlargement to the left. Despite oxygen, increasing cyanosis and dyspnea were observed from the second hospital day. The course was febrile and progressively downhill; death occurred on the fifth hospital day. Sulfapyridine had been administered during hospitalization.

CASE 31.—A.I.P. Accession 103378. A 28-year-old white man was hospitalized on the second day of an acute pharyngitis. The temperature was 100°F.; pulse rate, 90; and respirations, 22 per minute. The white blood cell count was 11,600. The pharyngitis subsided by the second day, but sulfathiazole was given for an infected umbilical sinus which had been draining for seven weeks. The latter improved considerably, but on the fifteenth hospital day the pharyngitis recurred. The temperature was initially 101.6°F.; the white blood count, 9,900. The fever mounted rapidly to 105.4°F., the pulse rate was 158, respirations were dyspneic, and blood pressure was 90/50. This state persisted, accompanied by drowsiness and mild diarrhea, and death occurred unexpectedly on the sixteenth hospital day.

CASE 32.—A.I.P. Accession 86959. A 25-year-old white man was admitted to the hospital on the second day of an acute nasopharyngitis. The temperature was 102°F.; pulse rate, 100; respirations, 20 per minute; and blood pressure, 118/60. The course was febrile, with temperatures ranging from 101° to 104° Fahrenheit. Pulse and respiratory rates gradually increased. Blood counts showed a relative leucopenia; the white blood cell count rose to a maximum of 16,000, but ranged between 8,000 and 12,000. Despite sulfathiazole and sulfadiazine, a pneumonic process originally limited to one lobe spread bilaterally. On the fifteenth day progressive weakness was observed; there were episodes of irrationality. Fatal pulmonary edema developed on the twenty-third day. At autopsy a streptococcal organism was isolated from the heart blood, the lungs, and the paranasal sinuses.

CASE 33.—A.I.P. Accession 93680. A 22-year-old white man returned to the hospital because of a pneumonic process four days after his release, after hospitalization for an acute upper respiratory infection. The temperature was 105°F. and the white blood cell count was 26,000. There were severe dyspnea and pleuritic pain. On oxygen and sulfathiazole therapy there was evident improvement. Although the fever subsided, pleural effusion developed on the third day. On the ninth day roentgenograms demonstrated partial resolution of the pneumonia, but there was enlargement of the heart. A soft to-and-fro murmur was present apically, and although there were no signs of cardiac failure, respirations were dyspneic, blood pressure was 104/58, and white blood cell count was 22,000. Electrocardiograms subsequently demonstrated myocardial damage and a heart rate of 146 per minute. Moderate left ventricular failure was diagnosed on the twelfth day. The temperature rose to 103°F. and the pulse rate to 90 per minute on the thirteenth day; the white blood count rose to 33,000 on the fifteenth day. Digitalization was undertaken on the seventeenth day when the patient presented dyspnea, orthopnea, and a pericardial friction rub. Heart action was irregular and rapid one day prior to death on the twenty-fourth hospital day.

CASE 34.—A.I.P. Accession 103357. A 24-year-old white man was hospitalized with a recurrence twenty-two days after a previous acute nasopharyngitis. The presenting symptoms included "chest pain." The temperature was 101.2°F.; pulse rate, 78 per minute; and respirations, 18 per minute. The heart and lungs were considered normal. Therapy consisted solely of sedatives which appeared to give relief. On the morning of the second hospital day the patient had a slight nose bleed and died suddenly of acute heart failure.

CASE 35.—A.I.P. Accession 157669. A 24-year-old white woman was hospitalized because of ankle edema. The patient had not felt entirely well since an acute "upper respiratory infection" two weeks previously. There had been orthopnea of one week's duration and constrictive sensation in the chest shortly before admission. The temperature was 98.6°F.; the pulse, 108; and the blood pressure, 94/82. Heart sounds were distant and the liver appeared enlarged. With bed rest the ankle edema subsided. On the sixth hospital day there was a sudden episode of vomiting, dyspnea, and cyanosis, associated with venous distention and swollen liver. An electrocardiogram indicated myocardial damage. A roentgenogram two days later showed the heart to be enlarged. White blood cell counts varied from 6,500 to 13,900. Blood cultures were sterile. Digitalization was instituted on the tenth day, but on the fifteenth day there was embolic occlusion of the right external iliac artery. Despite embolectomy, gangrene of the foot set in. Dyspnea and orthopnea persisted, the pulse remained poor, and death occurred on the twenty-fourth hospital day, thirty-eight days after the initial respiratory infection.

REFERENCES

1. Rantz, L., Boisvert, P. J., and Spink, W.: Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* 76:131, 1945.
2. Candel, S., and Wheelock, M. C.: Acute Nonspecific Myocarditis, *Ann. Int. Med.* 23:309, 1945.
3. Scherf, D.: Myocarditis Following Acute Tonsillitis, *New York M. Coll. & Flower Hosp. Bull.* 3:252, 1940.
4. Saphir, O.: Myocarditis: A General Review, With an Analysis of Two Hundred and Forty Cases, *Arch. Path.* 32:1000, 1941.
5. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, *Harvey Lect.* 35:251, 1940-1941.
6. Smadel, J.: Virus Division, Army Medical Center. Personal communication, May, 1946.
7. Rich, A.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarthritis Nodosa; Another Case Associated With Sulfonamide Reaction, *Bull. Johns Hopkins Hosp.* 71:375, 1942.
8. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, *Am. J. Path.* 18:109, 1942.
9. French, A. J.: Hypersensitivity in the Pathogenesis of the Histopathological Changes Associated With Sulfonamide Chemotherapy, *Am. J. Path.* 22:679, 1946.
10. Schenken, J. R., and Heibner, W. C.: Acute Isolated Myocarditis Due to a Streptococcus, *AM. HEART J.* 29:754, 1945.

ON THE ETIOLOGY OF CLUBBING OF THE FINGERS*

EDGAR F. MAUER, M.D.†
LOS ANGELES, CALIF.

IN MANY diseases clubbing of the fingers is a typical or an occasional feature, but the mechanism is disputed. Because of the uncertainty of pathogenesis and because of its diagnostic significance, this lesion has engaged the interest of physicians for a long time. Numerous theories of its causation have been proposed: toxic, neuritic, mechanical, static, anoxic, and so on. No theory has gained wide acceptance. Today the situation recalls one which led Osler to remark: "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future." This paper will attempt to take stock of known facts and indicate progress toward a final explanation for the mechanism of clubbing. The theory proposed is based on easily observed and generally accepted clinical data. It emphasizes the necessity for considering a cause of local anoxia which in the past has been disregarded, and points out a common basis for tissue anoxia in a galaxy of conditions in which cyanosis is not a feature. It is precisely this heterogeneous, apparently unrelated group of infections and neoplasms that gave rise to the abundance of theories when it appeared that the anoxia theory applicable in cyanotic heart disease was untenable in other conditions. If local anoxia can be shown to exist in these diseases, infections and neoplasms, it will make possible a return to a single pathogenic mechanism for clubbing of the fingers in a variety of diseases.

That clubbing exists in chronic arterial anoxia is an accepted fact. In congenital heart disease clubbing is seen only in the cyanotic group and in cyanose tardive only after the cyanosis has become established. When it is observed in other types of heart disease it is usually the result of chronic sepsis or severe pulmonary disease. In pulmonary emphysema clubbing occurs only when there is pronounced cyanosis or superimposed infection. Clubbing is present in individuals who for long periods of time have resided at high altitudes. It is also seen in some instances of aortic and subclavian aneurysms. Clubbing is also present in chronic methemoglobinemia, sulfhemoglobinemia, in enterogenous cyanosis,

Received for publication March 10, 1947.

*For simplicity of usage, this term shall include associated clubbing of the toes and pulmonary osteoarthropathy.

†From the Department of Medicine of the School of Medicine of the University of Southern California, and the Los Angeles County Hospital.

and in those chemical alterations in the hemoglobin which prevent its efficient use as a carrier of oxygen. In this respect these entities resemble somewhat the situation to be described, in which, however, interference with gaseous exchange is due to physical rather than chemical alterations which impair the usefulness of the hemoglobin. That anoxia exists in the conditions listed is apparent. However, tissue anoxia has not been recognized as a possible concomitant of infections and neoplasms. Yet it may be deduced that it exists in them, albeit the circulation is not obstructed and even in the finger tips cyanosis is not evident. It is the thesis of this paper that in certain infections and neoplasms in which clubbing makes its appearance, local tissue anoxia results from a peculiar physical state affecting the erythrocytes and evidenced by the increased sedimentation rate of the blood.

It is well known that the sedimentation rate of the blood is increased in infections and neoplasms in which clubbing exists: pulmonary tuberculosis; subacute bacterial endocarditis; bronchiectasis; empyema; lung abscess; chronic infections of the bowel, such as idiopathic ulcerative colitis, chronic dysentery, and regional enteritis; and in various neoplastic processes such as intestinal polyposis, bronchiogenic carcinoma, gastrointestinal malignancies, and large carcinomata of the breast. In the neoplastic lesions the elevated sedimentation rate is the result of tissue autolysis, infection, or both. But it is also recognized that clubbing does not occur in certain long-standing infections and in other lesions associated with increased sedimentation rates. These will be discussed.

The sedimentation rate of the blood, as an isolated phenomenon, is a reaction of a high degree of nonspecificity. The mechanism of the settling of the corpuscles is, however, of great importance. In general this acceleration is mainly a reflection of the level of the blood fibrinogen and, to a lesser extent, of the globulins.¹⁻³ The sedimentation rate varies directly with the concentration of these proteins. Increasing levels of the blood fibrinogen and globulin in some manner (altered colloidal state of plasma, changes in cellular charge, and so forth) cause the red cells to "stick together" and result in the formation of rouleaux. These aggregations of cells present to the surrounding fluid medium an increase in mass and a reduction in surface. This change and the reduction in the number of falling particles lead to increased rate of fall. (Other factors which influence the sedimentation rate are not germane and will be omitted from this discussion.)

Fahraeus¹ anticipated the question of the "biological importance" of rouleaux formation. "The qualification for this being the case is that the aggregations . . . at least under certain conditions . . . are an intravital phenomenon." In order to prove this he selected patients with increased sedimentation rates and demonstrated rapid settling of the red cells in artificially obstructed superficial veins. More important, he saw aggregates of red cells flowing through their retinal vessels and commented on the increased rate of flow in these individuals. At his suggestion, Ploman,⁴ an ophthalmologist, studied the character of the blood flow in retinal vessels while applying pressure to the eyeball for short periods. He was so impressed with his observations on clumping of cells *in vivo* that in 1920 he was impelled to write that he was "surprised that the peculiar

and striking picture . . . is not more generally observed and known." Foord⁵ described an identical observation in a patient with multiple myeloma in whom the marked *in vitro* rouleaux formation suggested the correct diagnosis. Fahræus also studied the capillaries of the nail fold. A uniform flow of blood was seen in normal individuals; in those with increased sedimentation rates, varying degrees of granularity were present and the flow of colored material was broken by stretches of clear plasma. Knisely,⁶ whose experience in the observation of the living circulation is extensive, states that in small laboratory animals rouleaux formation is not seen in the flowing blood "except under known pathological conditions such as ether anaesthesia, pressure or tension on the tissue, trauma, or preceding the death of the animal." Others also have observed this phenomenon *in vivo*. Wright and Duryee,⁷ observing clumps of cells in capillaries, considered this proof that capillaries may be much wider than generally supposed. It is of interest to note that Duken and von den Steinen⁸ not only observed granular flow but remarked on its presence in chronic pulmonary disease and in clubbing of the fingers. Ponder³ states that this capacity for aggregation presents a real transfusion hazard: "A greatly increased tendency to rouleaux formation in the blood of a recipient suffering from an acute infective condition may sometimes give rise to great difficulty in securing a proper crossmatch with the cells of a donor of the same blood group, for extensive rouleaux formation is produced by proteins of the recipient's serum. These rouleaux may be so large and so stable that severe reactions result." Clinical examples of the difficulties engendered by autoagglutination are described by Foord,⁵ Reiman,⁹ and Belk.¹⁰ Belk's experience led him to state that on occasion what was needed was "a different recipient, not a different donor." Thus it has been demonstrated that the erythrocytes of flowing blood are not always discrete structures, but may be bound together in rouleaux. We may now discuss their relation to tissue anoxia.

The biconcave configuration of the erythrocyte provides a structure admirably suited to its respiratory function. It results in the largest effective surface area in contact with plasma and facilitates efficient gaseous exchange. Individuals with normal sedimentation rates (normal fibrinogen, and so forth) have circulating red cells which are either discrete or form themselves into delicate rouleaux which disintegrate in the blood current. Thus, in health, the maximum cell surface area is made available for respiratory exchange. It is apparent that the functions of the red cells which have lost this ideal configuration by reason of aggregation into rouleaux will suffer in this regard. Gaseous exchanges at the periphery and perhaps in the lung will be interfered with in accordance with the number of cells in each clump, and, therefore, in proportion to the level of blood fibrinogen, and so forth, and the rate of sedimentation.

Fahræus,¹ in 1921, pointed out this result of altered suspension stability. "That which is of greatest interest from a physiological point of view is, of course, the state of the corpuscles within the capillary system where in the service of respiration they exercise their most important physiological function, the gas exchange. The gas exchange between the corpuscles on the one hand, and the tissues and the alveolar air on the other, takes place via the plasma. As the aggregation of the corpuscles reduces the surface between the corpuscles and the

plasma, we must a priori conclude that it affects the gas exchange of the corpuscles in an unfavourable manner." How unfavorable this reduction in surface may be can be realized by visualizing rouleaux which, when large, comprise many cells, their broad surfaces apposed, forming extensive ropes enclosing lakes of plasma. The degree of stability of the rouleaux is graphically presented by Fahraeus in his description of slide preparations. "In normal blood, the corpuscle rouleaux fall apart at the slightest movement in the fluid, while the aggregates in the rapidly settling blood are not disturbed until very violent currents are produced. The rouleaux are strained and stretched like rubber tubes before they break. It is almost impossible through pressure on the cover glass to obtain complete disaggregation. The aggregates are consequently not only larger in the rapidly settling blood, but have besides a decidedly more solid structure. Another characteristic difference is that the formation of new rouleaux after disaggregation proceeds very much faster in the last-named kind of blood than in normal blood." There are, then, two factors which influence the respiratory surface in this abnormal state of the blood: the size of the rouleaux and their frangibility.

It is apparent that the rouleaux must traverse the circulation and it is clear that if they are large enough and sufficiently stable they will obstruct capillaries. Transfusion reactions due to rouleaux have already been mentioned, and Fahraeus discusses their relation to thrombi in acute infections and eclampsia. Foord⁵ thought it possible that, in addition to the plugging of the tubules by protein in multiple myeloma, the obstruction of glomerular capillaries by clumping of red cells might contribute to the renal insufficiency of this disease. That rouleaux do exist in the flowing blood without causing obstructive phenomena has been observed and it is with this group that this paper is concerned. The comment of Wright and Duryee⁷ on capillary width has already been cited. Many investigators, among them Haldane among Priestley,¹¹ Hooker,¹² and Krogh,¹³ have pointed out the association of vasodilatation with anoxic states; and Mendlowitz¹⁴ in his studies of the peripheral blood flow in individuals with clubbing found it to be augmented. Charr and Swenson¹⁵ recently studied six instances of clubbing of the fingers and supplied pertinent data in five. Three patients with pulmonary tuberculosis came to autopsy, and the vessels of their hands were injected with radiopaque material. "The arteries and arterioles were more numerous, their lumens wider, and the ungual processes were covered with a heavier network of arterioles." Two patients, one with bronchiectasis and the other with congenital pulmonary stenosis, were studied by means of infrared photographs which revealed marked prominence of the superficial vessels. These accumulated observations indicate that the peripheral vascular bed is dilated in anoxic states and the arteriovenous anastomoses and bridges may well be utilized to accommodate the circulating rouleaux.

In recent years a new theory based on increased blood flow at the periphery has been proposed. Mendlowitz¹⁴ observed it in clubbing of the fingers occurring in the wake of congenital heart disease and infections, and described the accompanying vasodilatation. He concluded, in 1942,¹⁶ "that increased peripheral flow will form a cornerstone of the future theories on the mechanism of clubbing and hypertrophic osteoarthropathy." That this factor is important has already

been indicated. But it does not appear to be of initial importance, as without an anoxic factor clubbing does not occur. Clubbing is not seen during the course of hyperthyroidism, nor does it appear after sympathectomy. In view of the fact that dilated peripheral beds accompany anoxic states, it seems reasonable to assume that the increased peripheral flow observed by him is the result of vasodilatation secondary to the anoxia which exists in patients with clubbing. Mendlowitz and Leslie¹⁷ produced cyanosis in dogs by means of a venoarterial shunt (anastomosis between the pulmonary artery and the left auricle). In one animal, after an interval of eight months, periosteal proliferation was observed in the ulna. They concluded that they had produced hypertrophic osteoarthropathy and attributed it to the increased systemic flow incident to the shunt. They stated that arterial anoxemia existed, but concluded that anoxia was not the cause of the bone change because "transport of oxygen to the tissues was normal because of the increased blood flow and oxygen consumption remained unchanged." It does not seem permissible to ignore the anoxia observed in this experiment, since arterial anoxia is so definitely related to symptomatology in similar diseases of man in which tissue oxygen tension is reduced and in which clubbing is so commonly found. When clubbing of the fingers occurs in congenital heart disease, it does so only after cyanosis is manifest. Here it is hardly conceivable that the delivery of oxygen to the tissues is unchanged. Rather, increased peripheral flow is a response to the anoxic state of the blood and tissues. More direct evidence is found in the observations of Blalock and Taussig¹⁸ that clubbing recedes in their patients operated on for the tetralogy of Fallot. Certainly this recession cannot be attributed to reduced peripheral flow, per se, incident to deflection of blood from the arterial system to the pulmonary artery. Obviously another factor must be operative, and it would appear reasonable to assume that the remarkable increase in oxygen saturation and the amelioration of dyspnea and cyanosis must be related to the reversal of clubbing seen in these subjects. The same reversal of clubbing occurring when individuals remain at sea level after prolonged residence at high altitudes is another expression of the role of increased oxygen tension in the tissues. Nevertheless, increased peripheral flow is an important factor in the production of clubbing in which the tissue anoxia is due to rouleaux formation. It may be that, due to the increased rate of flow, the rouleaux pass through the tips of the extremities with such rapidity that they do not have time to diffuse out their oxygen content. It is possible that many of the rouleaux escape through the arteriovenous anastomoses which are so numerous in these locations. The finger tips of subjects with clubbing are warm, and the factors of tissue warmth, speed of flow, and rouleaux formation all seem to be concerned with the delivery and uptake of oxygen by the tissues. As will be shown, tissue anoxia with cold finger tips and slow rates of flow is not conducive to clubbing.

In chronic rheumatoid arthritis the sedimentation rate is increased over periods of years and clubbing is not observed. But here, peripheral vasoconstriction and cold finger tips are the rule and the sluggish flow may be adequate to maintain oxygen tension in the acral tissues with low metabolic levels. More difficult to explain is the absence of clubbing in Raynaud's disease and Buerger's

disease, where chronic anoxic injury is only too apparent. But in these conditions as well the tissue temperatures are low and the blood flow is diminished. These stand in contrast to the conditions in which clubbing develops and in which the fingers and toes are warm and the blood flows are rapid. Whether such a mechanism is responsible for the rarity of clubbing in multiple myeloma cannot be stated at this time.

That clubbing of the fingers does not occur in anemia has been pointed out by critics of the anoxia theory. Anemia of a degree sufficient to cause tissue anoxia rarely persists for a long period of time, and it is well known that only the most severe anemias are associated with dyspnea at rest. In the absence of infection, the circulating red cells are discrete, exposing their entire surfaces to the plasma, or exist in the form of delicate, easily disintegrated rouleaux. Furthermore, in anemia the compensatory mechanisms are highly efficient. There is increased cardiac output, circulation rate, and local vasodilatation. The cells are fully saturated with oxygen in the lungs and by virtue of increased volume of flow are permitted to deliver it at effective pressure. Such protective mechanisms are of little value in conditions which prevent normal uptake and delivery of blood gases by the red cells. Chronic methemoglobinemia and sulfhemoglobinemia, rather than anemia, may be compared with the rouleaux effect and here again clubbing is observed.

Granting the preceding effects of rouleaux, of increased peripheral flow, and of shunts between arterioles and venules which are most numerous in the extremities, local tissue anoxia may exist in infections and neoplasms in which the red cells readily form rouleaux. It is to be expected that tissue alteration incident to such a mechanism would be influenced not only by the degree of physical alteration of the blood, but by the length of time during which it is operative, and undoubtedly by the degree of continuity of the process. This concept is of importance, since it probably explains the failure of clubbing to occur in all instances of a particular disease.

As has been stated, the "toxic" and "infectious" theories have been discarded, and properly so. Nevertheless, clubbing of the fingers is frequently associated with chronic infections. It has been seen to vary with the intensity of the underlying process, and indeed, has disappeared completely when cure has been attained. As one peruses a compilation of chronic infections in which clubbing has been described, he encounters lesions of diverse etiologies involving almost every system. Even the liver fails to escape inclusion; it is noteworthy that clubbing is described in cholangiolitic processes but is rarely found in cirrhosis, a lesion in which fibrinogen production is impaired.

The mechanism just described accounts for the production of clubbing of the fingers on a basis of tissue anoxia rather than on the transparent fact that intoxication is present. The arguments which have been used against the toxic theory seem to substantiate the mechanism proposed. It has been said that clubbing does not occur in chronic osteomyelitis unless there is amyloid disease. It has been suggested that here the clubbing is due to the amyloidosis. It seems more probable that the amyloidosis and the clubbing are both incident to the same process and both may be related to the high levels of plasma fibrinogen and

globulin. The theory proposed herein serves to explain the failure of clubbing to appear uniformly in infections of long standing. Instances of tuberculosis and bronchiectasis of many years' duration have been observed in which clubbing is not present. These are the individuals with little or no systemic reaction, low fibrinogen and globulins, and normal sedimentation rates.

It may well be asked whether clubbing of the fingers is the sole manifestation of chronic anoxia in conditions characterized by increased rouleaux formation. Individuals with severe cyanosis due to heart disease, and so forth, and those suffering from chronic mountain sickness, adapt themselves to the lower oxygen tensions of their blood. Yet in this process adaptation is only relative. In addition to clubbing they suffer from other symptoms of anoxia, such as dyspnea on exertion, loss of strength, easy fatigability, gastrointestinal disturbances, and certain psychologic abnormalities. Whether some of the poorly understood general symptoms of chronic diseases are related to the anoxic state invites further investigation. Since the time of Bert,¹⁹ various students of anoxia have felt that in addition to the demonstrable cardiac, hemic, and respiratory adjustments of acclimatization, a tissue factor exists which permits satisfactory function at lower levels of oxygen saturation. Haldane and Priestley¹¹ state that despite lack of experimental verification there are facts which indicate the validity of this theory. Of morbus caeruleus they write "It seems hardly possible to doubt, therefore, that their tissues have become adapted to the low partial pressure of oxygen; and the same adaptation probably exists in many chronic cases of valvular heart disease, emphysema, etc." As Henderson²⁰ has succinctly written: "There are as many acclimatizations as there are altitudes at which a man can live." In infections and neoplasms a similar latitude of adaptation exists.

Proof of this theory appears as difficult now as in 1923 when Lundsgaard and Van Slyke²¹ bemoaned the difficulties encountered in the determination of tissue gas tensions. This factor is crucial in relation to the theory postulated. Isolated observations of the sedimentation rates and blood protein patterns are of little value. Therefore, no clinical observations are appended. Such as have been made seem to agree with the theory proposed. Unidigital and congenital clubbing are not discussed, since the author has not had the opportunity to study examples of these conditions.

SUMMARY

Clubbing of the fingers and toes, and the more severe "pulmonary" osteoarthropathies and periostitides, occur when there is arterial anoxia due to congenital or acquired lesions or residence at high altitude. It occurs in many disorders in which the erythrocyte sedimentation rate is rapid, but arterial oxygen saturation normal. In all these cases the vascular bed is wide, blood flow rapid, and the tissue warmer than normal.

That rapid sedimentation rates, with intravascular rouleaux formation, interfered with oxygenation of the tissues by decreasing the diffusion surface per unit of hemoglobin had long ago been suggested by Fahraeus. In this review it is suggested that with escape of rouleaux through the arteriovenous anastomoses

so numerous in the fingers and toes, rapid blood flow and high levels of arterial and venous oxygen saturation may be present simultaneously with low oxygen tension in the digital tissues. Thus, rapid rates of blood flow and low tissue oxygen tension would provide the same mechanism for clubbing in chronic infections, neoplasms, or metabolic defects leading to abnormal fibrinogen and globulin levels, as in the classical cases of arterial anoxia.

The most rapidly evolving and the most severe types of osteoarthropathy are seen in cases of mediastinal and lung tumors where the sedimentation rates are rapid and arterial anoxia is present. Here the two types of anoxia may coexist.

In rheumatoid arthritis, in Raynaud's disease, and in Buerger's disease clubbing is rare, although tissue anoxia is severe in the latter two and rapid sedimentation rates are characteristic of the former. But in all of these, blood flow and tissue temperatures are low in the tips of the extremities. It is thereby concluded that for the development of clubbing low oxygen tensions must occur in tissues which are warm and in which the blood flow is greater than normal.

For helpful suggestions and criticism the author wishes to express his appreciation to Dr. William Dock.

REFERENCES

1. Fahraeus, R.: The Suspension Stability of the Blood, *Acta med. Scandinav.* 55:1, 1921.
2. Ham, T. H., and Curtis, F. C.: Sedimentation Rate of Erythrocytes, *Medicine* 17:447, 1938.
3. Ponder, E.: *Medical Physics*, Chicago, 1944, The Year Book Publishers, Inc., p. 1412, p. 1414.
4. Ploman, K. G.: Stability in Suspension of Blood Corpuscles, *Hygiea* 82: 363, 1920, cited by Fahraeus, R.¹
5. Foord, A. G.: Hyperproteinemia, Autohemagglutination, Renal Insufficiency, and Abnormal Bleeding in Multiple Myeloma, *Ann. Int. Med.* 8:1071, 1935.
6. Knisely, M. H.: Spleen Studies. II. Microscopic Observations of the Circulatory System of Living Traumatized Spleens, *Anat. Rec.* 65:131, 1936.
7. Wright, I. S., and Duryee, A. W.: Human Capillaries in Health and in Disease, *Arch. Int. Med.* 52:545, 1933.
8. Duken, J. and von den Steinen, R.: Das Krankheitsbild der Bronchiektasie im Kindesalter, *Ergebn. d. inn. Med. u. Kinderh.* 34:457, 1928, cited by Wright and Duryee.⁷
9. Reimann, H. A.: Hyperproteinemia as Cause of Autohemagglutination; Observations in a Case of Myeloma, *J. A. M. A.* 99:1411, 1932.
10. Belk, W. P.: The Minor Blood Agglutinins and Their Relation to Post Transfusion Reactions, *Am. J. M. Sc.* 191:827, 1936.
11. Haldane, J. B. S., and Priestley, J. G.: *Respiration*, New Haven, 1935, Yale University Press, p. 398.
12. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, *Physiol. Rev.* 1:112, 1921.
13. Krogh, A.: *The Anatomy and Physiology of the Capillaries*, New Haven, 1929, Yale University Press.
14. Mendlowitz, M.: Some Observations on Clubbed Fingers, *Clin. Sc.* 3:387, 1938.
15. Charr, R., and Swenson, P. C.: Clubbed Fingers, *Am. J. Roentgenol.* 55:325, 1946.
16. Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy, *Medicine* 21:269, 1942.
17. Mendlowitz, M., and Leslie, A.: Experimental Simulation in the Dog of the Cyanosis and Hypertrophic Osteoarthropathy Which Are Associated With Congenital Heart Disease, *Am. HEART J.* 24:141, 1942.
18. Blalock, A., and Taussig, H. V.: The Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, *J. A. M. A.* 128:189, 1945.
19. Bert, P.: *La Pression Barometrique*, 1878. Cited by Van Liere, E. J.: Anoxia. Its Effect on the Body, Chicago, 1942, University of Chicago Press, p. 143.
20. Henderson, Y.: *Adventures in Respiration*, Baltimore, 1938, Williams & Wilkins Company, p. 76.
21. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine* 2:1, 1923.

INHIBITION OF PAROXYSMAL VENTRICULAR TACHYCARDIA BY ATROPINE

M. WILBURNE, M.D., A. SURTSHIN, M.D., S. RODBARD, M.D.,
AND L. N. KATZ, M.D.

CHICAGO, ILL.

IT HAS been recognized that paroxysmal ventricular tachycardia can be induced by chloroform and by cyclopropane anesthesia in man. It can also be induced in animals anesthetized with these agents, especially after administration of sympathomimetic drugs.¹⁻⁵ The subject has been extensively reviewed by Meek^{6,7} and it has continued to be the basis of more recent work.^{8,20}

In the course of certain studies on the effects of sympatholytic agents in trained unanesthetized dogs we noted that the intravenous injection of epinephrine produced paroxysmal ventricular tachycardia. Because of the simplicity of the method and the advantages which we obtained by studying the effect of this ectopic initiating mechanism of epinephrine, we undertook a study of certain aspects of ventricular tachycardia. Attention was directed especially to the prophylactic benefits of atropine.

METHODS

Thirty-two experiments were performed on eleven young and mature dogs weighing 6.4 to 29.5 kilograms. Two had Goldblatt renal artery clamps and nine were unoperated. These dogs had been trained for a period of months to lie quietly while a needle was being inserted in the femoral artery and blood pressure was being recorded. Accordingly, the administration of the injections occasioned no observable discomfort or excitement in the animals. Electrodes were applied to shaved areas on the legs and electrocardiographic records were obtained with a string electrocardiograph; Lead II was used. After a control reading, a needle was inserted cephalad into the foreleg vein and a few cubic centimeters of normal saline were injected. After ten to thirty seconds the syringe was exchanged for one containing 1.0 mg. of epinephrine hydrochloride in 5.0 c.c. of normal saline and the solution was injected rapidly. A continuous recording was made of the period before, during, and for several minutes after the injection of epinephrine. A signal on the record indicated the beginning and end of injection.

From the Cardiovascular Department, Research Institute, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast Fund for Cardiovascular Research.

This department is supported in part by the Michael Reese Research Foundation.

Received for publication March 14, 1947.

RESULTS

The Effects of Epinephrine.—The results are summarized in Table I. During the intravenous injection of epinephrine a rise in blood pressure occurred. Within twenty or thirty seconds the dog licked its lips and showed some signs of apprehension. At this time a slowing of the heart appeared, doubtlessly due to a reflex from the carotid sinus moderator mechanism (Fig. 1). The dog then appeared to relax and sometimes became apneic for ten to twenty seconds. In from 2 to 180 seconds after the end of injection, usually when the blood pressure showed signs of leveling off or had begun to decline, the marked reflex vagal bradycardia, which was often associated with sinus bradycardia (Figs. 2 and 7), sinus

TABLE I. DATA ON EPINEPHRINE-INDUCED PAROXYSMAL VENTRICULAR TACHYCARDIA

DOG	WEIGHT (KG.)	EXPT. NO.	DURATION OF EPINEPHRINE INJECTION (SEC.)	TOTAL DURATION OF EPINEPHRINE- INDUCED VENTRICULAR TACHYCARDIA (SEC.)
A	15.5	1	13.0	302
		2	8.0	11
		3	4.0	79
B	29.5	1	6.0	94
		2	10.5	70
		3	9.5	30
C	8.4	1	14.0	71
		2	4.5	168
		3	16.5	112
D	13.2	1	8.0	18
		2	4.0	30
		3	7.0	36
E	10.0	1	4.5	188
		2	7.5	47
		3	12.0	29
F	14.5	1	10.0	133
G	15.0	1	5.0	19
		2	4.5	54
		3	8.0	0
		4	3.5	31
H	15.2	1	7.0	42
		2	4.0	65
		3	14.0	0
		4	14.0	0
		5	7.5	52
I	6.4	1	12.5	0
		2	5.0	252
		3	4.5	187
J	14.1	1	13.0	0
		2	3.5	0
K	26.4	1	14.0	0
		2	4.0	0

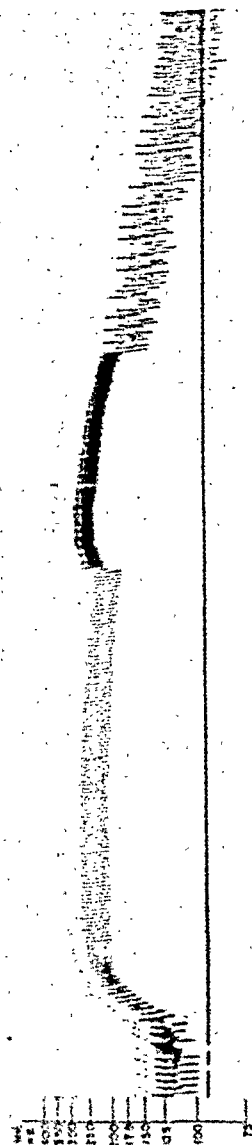


Fig. 1.—Blood pressure response to intravenous injection of 1.0 mg. epinephrine. Injection period indicated by interruptions of base line. Note the slow development of the primary rise in pressure associated with slowing of the heart rate, in contrast with the sudden onset of the secondary rise in blood pressures followed in a beat or two by the paroxysm of ventricular tachycardia. At the end of the paroxysm the pressure falls abruptly, and continues downward below control levels. After a variable period of five to fifteen minutes, the pressure returns to approximately control values (not shown). Calibration in mm. Hg shown at left. Time in seconds below.

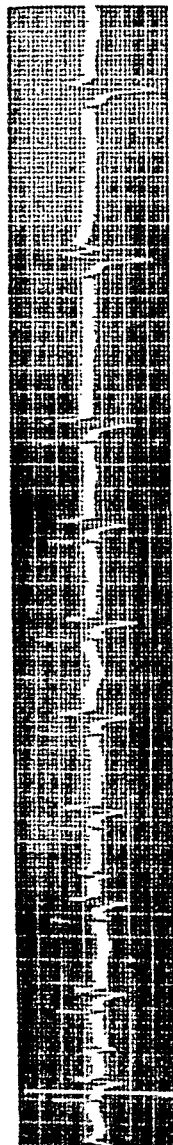


Fig. 2.—Electrocardiogram (Lead II) following the intravenous administration of 1.0 mg. of epinephrine showing a progressively increasing inhibition of the sinus node. The white line interrupting the curve denotes completion of the injection. The progressive increase in the P-P interval is clearly seen. The third auricular complex is followed by a five second interval of auricular standstill. The last P wave is merged with the T wave of the second to last beat. The P waves vary in contour. Complete A-V block began during the epinephrine injection. Idioventricular rhythm shifts to a new and slower pacemaker in the last two beats.



Fig. 3.—Electrocardiogram (Lead II) taken during and after the intravenous injection of 1.0 mg. of epinephrine. Prior to, and for several beats following, the termination of the injection (indicated by the white line) a sinus arrhythmia is present. This is followed by a shift in the sinus pacemaker which in turn is superseded by a sinus tachycardia (rate 158 to 170) with a differently contoured P wave, and complete A-V block with an idioventricular pacemaker which shifts in location (rate 52).

standstill (or S-A block) and nodal escapes (Fig. 5), and partial or complete A-V block (Figs. 2, 3, 4, and 6), gave way suddenly to a paroxysm of ventricular tachycardia (Fig. 7). This either was continuous or occurred in bursts (intermingled on occasion with single ventricular premature systoles), with a rate generally of about 200 to 220 beats per minute, although rates faster than this were encountered (Fig. 7). At this time the blood pressure showed a sharp secondary rise (Fig. 1). This rise sometimes preceded or coincided with the ventricular tachycardia. When the ventricular tachycardia was intermittent, it was interspersed with sinus or nodal tachycardia at a rate only slightly slower than the ventricular tachycardia. The ventricular tachycardia generally developed within 1 to 2 minutes, and persisted for from eleven seconds to five minutes. The animals often retched or vomited during this period. During the period of ventricular tachycardia, or just before, a marked tachypnea usually developed, with respiratory rates rising to about 300 per minute (Fig. 6). After cessation of the ventricular tachycardia a brief period of bradycardia, with or without the arrhythmias observed in the pretachycardia period, frequently occurred. This was soon replaced by a sinus tachycardia. In some instances the sinus tachycardia followed at once after the ventricular tachycardia.

Susceptibility to the occurrence of ventricular tachycardia appears to vary in different animals. This coincides with the experience of Meek and associates.⁴ However, ventricular fibrillation was not induced in any of our animals. The susceptibility to ventricular tachycardia could not be related to the age or the sex of the dog, or to the slight variations in dose or rate of injection. Nevertheless, it is possible that larger dose or faster rates of injection might have increased the percentage of successful trials. Because of the rapid destruction it is apparent that the slow injection of epinephrine is equivalent in many respects to reduction in dosage.

The Effect of Atropine.—The intravenous administration of 1.3 mg. of atropine sulfate to seven of our trained unanesthetized dogs was followed within one minute by a sinus tachycardia (Fig. 8), the rate rising to about 250 to 290 per minute. Respiration became more rapid, the pupils dilated, and there was dryness of the oral mucosa.

The Inhibition of Ventricular Tachycardia by Atropine.—The results are given in Table II. One to five minutes following the administration of atropine, the administration of 1.0 mg. of epinephrine resulted in a rise in blood pressure and the heart rate increased to rates of about 300 per minute (Fig. 9). The reflex bradycardia after epinephrine previously seen was now absent. Retching and vomiting occurred. In only one out of nine trials in seven dogs was a run of ventricular tachycardia observed. In this exception, the dog, which was the largest in our series (and, therefore, received the smallest dosage per kilogram), exhibited a run of ventricular tachycardia which persisted for forty-four seconds.

As can be seen by comparing Tables I and II, each of the animals was tested to determine that it was capable of responding to the epinephrine by the appearance of ventricular tachycardia. All had given three positive control responses to epinephrine in the absence of atropine.

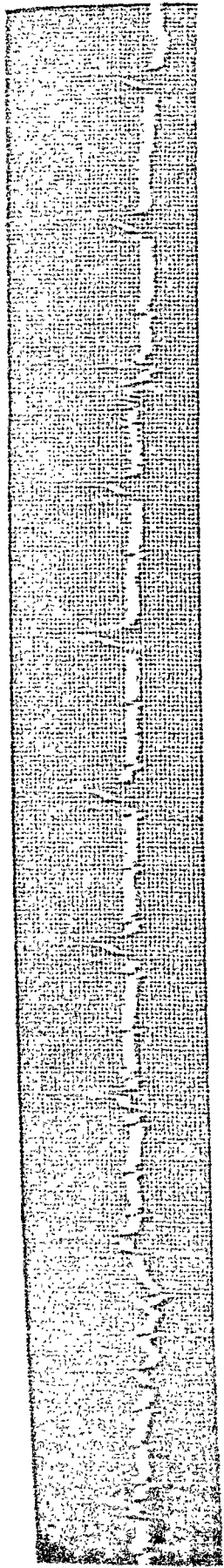


Fig. 4.—Electrocardiogram (Lead II) taken immediately after the administration of 1.0 mg. of epinephrine intravenously showing persistence of sinus tachycardia (rate 170) and complete A-V block (ventricular rate 48). Subsequent progressive slowing of the sinus pacemaker occurs with final disappearance of the P waves. This is associated with a shifting (and slowing) of the idioventricular pacemaker. The oscillations toward the end of the record are extracardiac artefacts.

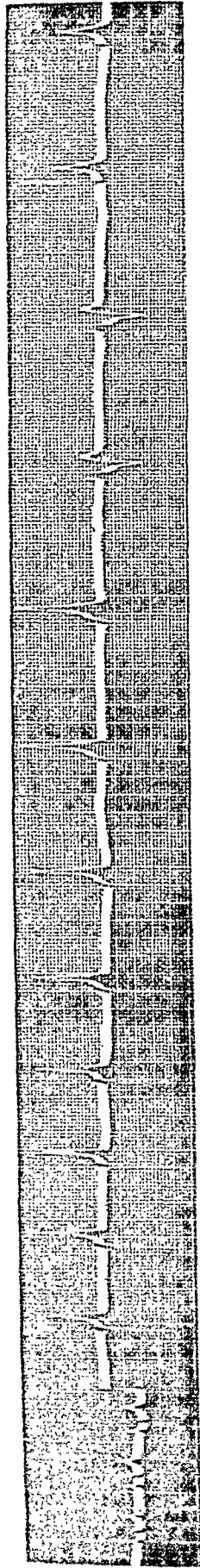


Fig. 5.—Electrocardiogram (Lead II) taken immediately after the intravenous injection of 1.0 mg. of epinephrine showing an abrupt arrest of the sinus node, followed by the assumption of pace maker function by an idioventricular pacemaker and progressive slowing of the latter. The site of the ventricular impulse formation varies.

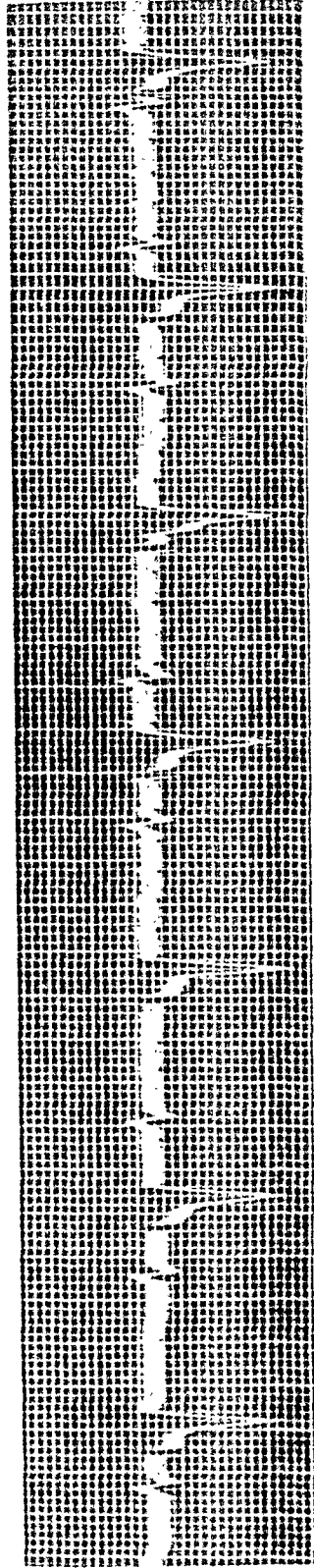


Fig. 6.—Electrocardiogram (Lead II) taken immediately after the intravenous injection of 1.0 mg. of epinephrine showing sinus arrhythmia and complete A-V block with an idioventricular pacemaker arising from one focus. The auricular rate averages 86, the ventricular rate, 57 per minute. In the second half of the curve are regularly spaced, very small upright deflections resembling P waves. Pneumographic records have shown these to represent the marked post-apneic tachypnea frequently observed after intravenous administration of epinephrine. Temporary slowing of the timer lines occurs in the last portions of the record.

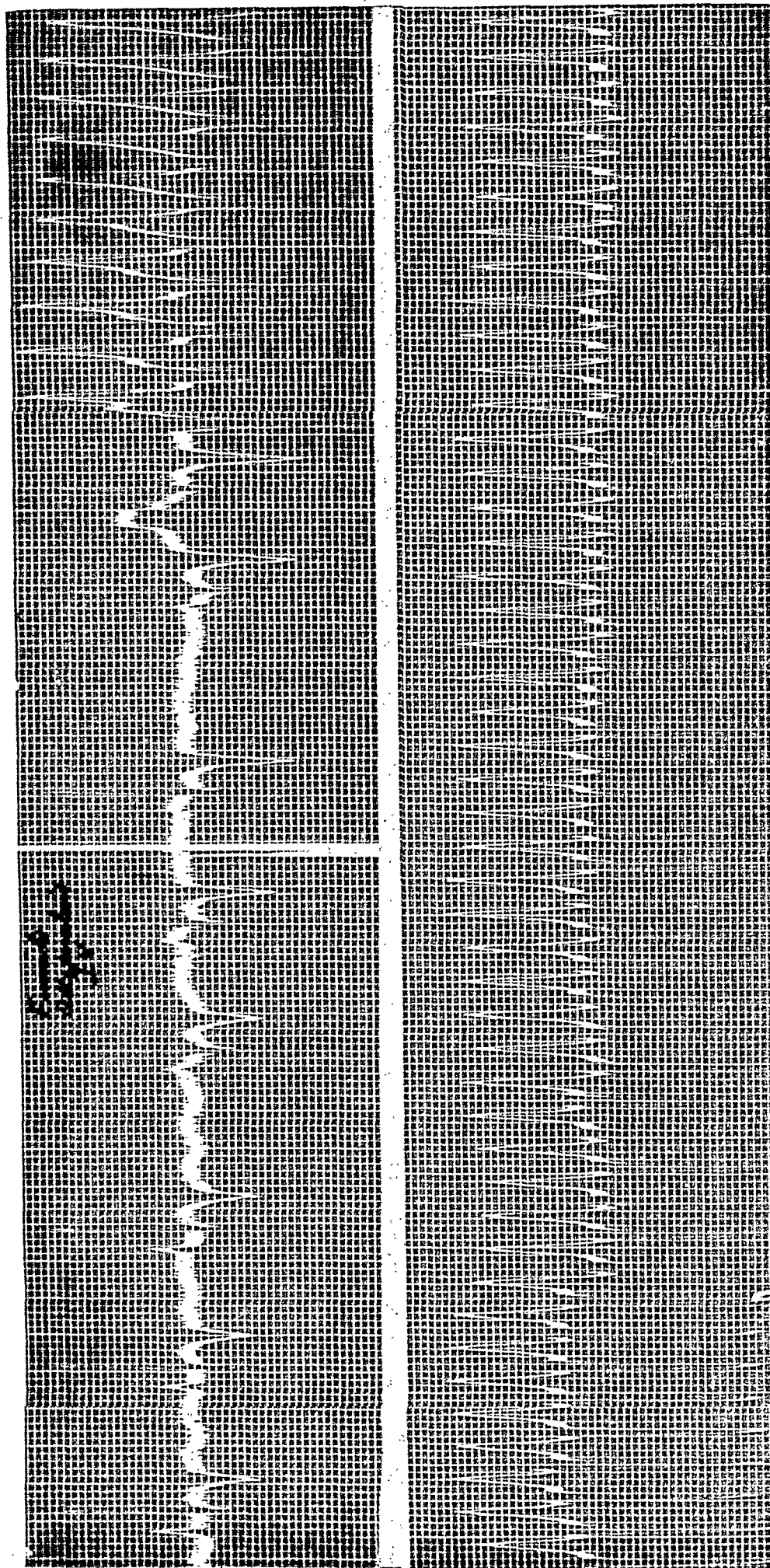


Fig. 7.—Electrocardiogram (Lead II) taken during and after the administration of 1.0 mg. epinophrine. The white line in the upper strip indicates the completion of the injection. Note the abrupt onset of ventricular tachycardia. The ventricular rate at the beginning of the paroxysm is 270 per minute. In the lower strip taken during the height of the paroxysm the rate is 330.

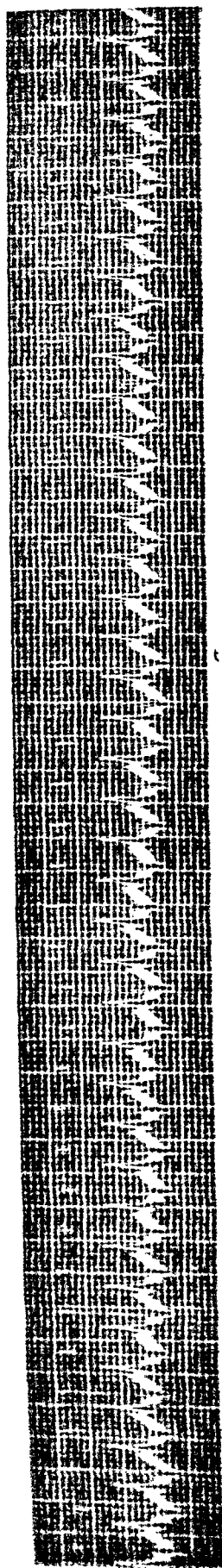


Fig. 8.—Electrocardiogram (Lead II) showing a sinus tachycardia with a rate of 270 per minute following the intravenous administration of 1.3 mg. of atropine.

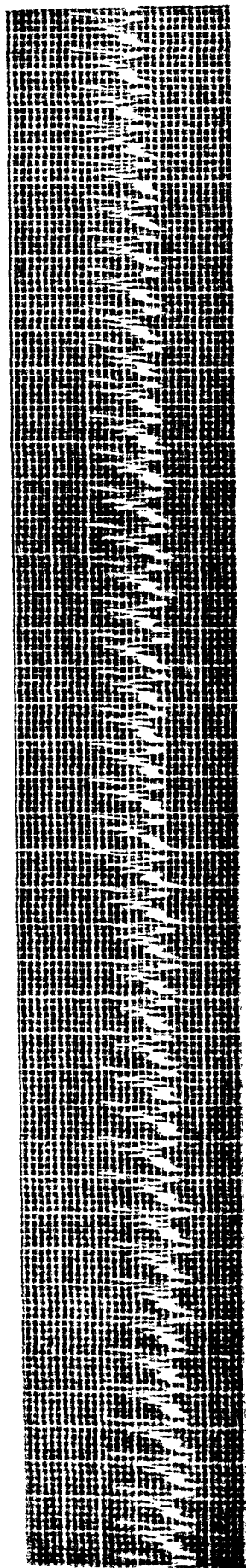


Fig. 9.—Electrocardiogram (Lead II) showing a sinus tachycardia with a rate of 300 per minute following the intravenous administration of 1.0 mg. of epinephrine to an atropinized dog (the same animal illustrated in Fig. 8). The prevention of ventricular tachycardia by the latter drug in this animal may result from retention of pacemaker function by the sinus node, since its rate of discharge is more rapid than that of the potential ventricular focus. This explanation does not apply to all animals.

TABLE II. EFFECT OF ATROPINE IN PREVENTING EPINEPHRINE-INDUCED PAROXYSMAL VENTRICULAR TACHYCARDIA

DOG	DURATION OF ATROPINE INJECTION (SEC.)	INTERVAL AFTER ATROPINE AT WHICH EPINEPHRINE WAS ADMINISTERED (SEC.)	DURATION OF EPINEPHRINE INJECTION (SEC.)	TOTAL DURATION OF PAROXYSMAL VENTRICULAR TACHYCARDIA (SEC.)
A	14.0	68	10.0	0
B	14.0	78	8.0	44
C	8.5	63	14.0	0
D	8.5	100	4.5	0
E	10.0	111	7.0	0
G	45.0	300	7.0	0
	5.5	100	4.0	0
H	15.0	300	15.0	0
	22.5	112	5.0	0

DISCUSSION

It is well known that epinephrine increases the rate of the isolated heart. This is not always seen in the intact unanesthetized animal. Instead, a slowing of the heart occurs due to a reflex from the carotid sinus and the aortic depressor mechanism acting over the vagi. Also, because of this moderator mechanism, the blood pressure rise is modified and reduced. If the dose of epinephrine is sufficient to overcome this moderator mechanism, at least for a time, the pressor and cardiac accelerating actions of epinephrine may lead to a sudden rise in pressure and heart rate to the levels which would have been obtained had it not been for the moderating secondary mechanisms. At this time the stimulation of ectopic pacemakers which epinephrine causes, combined with the depression of the sinus node, may permit the development of paroxysmal ventricular tachycardia.

Our observation that atropine tends to prevent experimentally induced paroxysmal ventricular tachycardia is in accord with previous observations (Petzetakis and Vlachlis, ^{1,10,11}) who found that atropinization prevented the occurrence of conduction disturbances induced by epinephrine in the rabbit. Seevers and associates⁹ noted in dogs that atropine raised the level of cyclopropane concentration necessary to cause ectopic ventricular rhythm. Akita² recently reported that atropinization, bilateral vagotomy, or bilateral resection of the depressor nerves prevented the occurrence of epinephrine-induced ectopic ventricular rhythms in the rabbit. Hoff and Nahum³ found vagotomy in cats lightly anesthetized with sodium amytal usually prevented epinephrine-induced ventricular rhythms. Shen¹² found that bilateral vagotomy and carotid sinus denervation gave protection against benzol-epinephrine-induced ventricular

fibrillation. However, Allen and associates⁸ found that bilateral vagotomy did not abolish ventricular tachycardia induced by cyclopropane in fifteen out of nineteen cats. They also found in eight cats that atropine in doses of 0.02 to 0.2 mg. per kilogram subcutaneously also failed to prevent the ventricular arrhythmia.

Hoff and Nahum³ attributed their results to a synergistic action of vagotomy and epinephrine in raising the rate of the sinus pacemaker to a level exceeding that of the potential rate of the ventricular ectopic pacemaker. This enhancement of the sinus rate keeps the ectopic pacemaker suppressed and prevents it from "escaping" and assuming control of the ventricles. In our experiments, also, four of six dogs showed a rate of the sinus node after atropine and epinephrine faster than that of the ventricular tachycardia induced by epinephrine alone (using the shortest cycles in the measurements). This tends to support the view of Hoff and Nahum.

This, however, need not be the mechanism involved. It may be that the ectopic ventricular rhythm is a vagus effect. It occurs in the midst of the vagal bradycardia and it is abolished by atropine at the same time as the bradycardia. In support of this view, the work of Otto and Gold¹³ may be mentioned. They found in a patient predisposed to spontaneous supraventricular paroxysmal tachycardia that these attacks of rapid heart action could be induced by epinephrine. Atropine sulfate (4.0 mg. subcutaneously) administered over a period of twenty minutes could prevent the epinephrine-induced tachycardia. Under atropine, the sinus rate ranged from 106 to 132 per minute and yet the ectopic pacemaker, having a rate of 200 or more, was inhibited. The mechanism suggested by Hoff and Nahum³ can not be invoked in such a case, nor can it be invoked in two of our six dogs in which the sinus rate after atropine and epinephrine was slower than that of the ventricular tachycardia induced by epinephrine alone.

The concept that epinephrine acts reflexly to produce both the bradycardia and ectopic rapid ventricular beating is supported indirectly by the signs of reflex or direct central nervous system stimulation in the form of tachypnea, retching, and vomiting which follow epinephrine administration. Recently, evidence has accumulated that chlorinated hydrocarbons, which also cause ventricular tachycardia, operate via the central nervous system and act through the acetylcholine esterase system.¹⁴ It has been shown by Beattie, Brow, and Long¹⁵⁻¹⁶ that direct stimulation of the hypothalamus may lead to the appearance of ventricular premature systoles. Atropine, by its effect on the acetylcholine esterase system, would interfere with such reflex cholinergic actions of epinephrine.

It has been shown by LeRoy, Fenn, and Gilbert¹⁷ that atropine reduces the mortality rate from 70 per cent to 34 per cent in dogs anesthetized by morphine and nembutal, and to 50 per cent in unanesthetized dogs in which the anterior descending branch of the left coronary artery had been previously ligated. Death in all animals, whether atropinized or not, was due to ventricular fibrillation. Studies such as this have been the basis of the clinical use of atropine in recent myocardial infarction. From the results of our studies and those of others cited,

atropine would appear to act on the acetylcholine-cholinesterase mechanism to prevent reflex vagal-induced ventricular premature systoles, paroxysmal tachycardia, and fibrillation. The concept that atropine abolishes a vagal coronary vasoconstriction¹⁷ is not supported by the work of this laboratory (Mintz and Kondo,¹⁸ and Katz and Jochim¹⁹).

SUMMARY

1. The rapid intravenous injection of epinephrine provides a simple and effective method for the experimental production of ventricular tachycardia in the intact, unanesthetized animal.

2. Utilizing this procedure, it was found that 1.3 mg. of atropine sulphate administered intravenously prevented the development of ventricular tachycardia. Apparently this is due, on occasion, to the action of atropine in permitting the sinus node to discharge at a rate more rapid than that of the ventricular focus, the former, thereby, retaining its pacemaker function. Not all cases can be explained in this way, however. It would appear that atropine operates also on the acetylcholine esterase system to prevent reflex cholinergic actions of epinephrine.

3. Atropine would appear to be of value in preventing ventricular tachycardia and maintaining a sinus tachycardia. This is of particular importance in myocardial infarction where the evolution of recent ventricular tachycardia to fibrillation may be averted.

4. It is suggested that the recently observed beneficial effects of atropine in lowering mortality in experimental coronary artery ligation may be due in large part to its prevention of ventricular tachycardia and terminal ventricular fibrillation.

REFERENCES

1. Petzetakis, M.: The Action of Intravenous Injection of Epinephrine on Cardiac Rhythm in the Rabbit, *Electrocardiographic Study*, *J. de physiol. et de path. gén.* **29**:428, 1938.
2. Akita, T.: Influence of Vagus and Depressor Nerves on Disturbances of Cardiac Conductivity and Rhythm Produced by Administration of Epinephrine in Rabbits, *Folia pharmacol. japon. (Brev.)* **26**:95, 1938.
3. Hoff, H. E., and Nahum, L. H.: The Role of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl-B-Methylcholine, *J. Pharmacol. & Exper. Therap.* **52**:235, 1934.
4. Meek, W. J., Hathaway, H. R., and Orth, O. S.: The Effects of Ether, Chloroform and Cyclopropane on Cardiac Automaticity, *J. Pharmacol. & Exper. Therap.* **61**:240, 1937.
5. Orth, O. S., Leigh, M. D., Mellish, C. H., and Stutzman, J. W.: Action of Sympathomimetic Amines in Cyclopropane, Ether and Chloroform Anesthesia, *J. Pharmacol. & Exper. Therap.* **67**:1, 1939.
6. Meek, W. J.: Some Cardiac Effects of the Inhalant Anesthetics and the Sympathomimetic Amines, *Harvey Lect.* **36**:188, 1940.
7. Meek, W. J.: Cardiac Automaticity and Response to Blood Pressure Raising Agents During Inhalation Anesthesia, *Physiol. Rev.* **21**:324, 1941.
8. Allen, C. R., Hoeflich, E. A., Cooper, B. M., and Slocum, H. C.: Influence of the Autonomic Nervous System Upon Spontaneous Cardiac Arrhythmias During Cyclopropane Anesthesia, *Anesthesiology* **6**:261, 1945.

9. Seevers, M. H., Meek, W. J., Rovenstine, E. A., and Stiles, J. A.: A Study of Cyclopropane Anesthesia With Especial Reference to Gas Concentrations, Respiratory and Electrocardiographic Changes, *J. Pharmacol. & Exper. Therap.* 51:1, 1934.
10. Petzetakis, M.: The Predominant Vagotropic Action of Adrenalin, *Arch. d. mal. du coeur* 19:513, 1926.
11. Petzetakis, M., and Vlachlis, G.: Electrocardiographic Study of the Vagotropic Action of Adrenalin, *Arch. d. mal. du coeur* 23:333, 1930.
12. Shen, T. C. R.: Benzol-Adrenaline Cardio-ventricular Fibrillation and Methods of Prevention, *Arch. internat. de pharmacodyn. et de therap.* 61:43, 1939.
13. Otto, H. L., and Gold, H.: Auricular Paroxysmal Tachycardia: The Effect of Epinephrine, Quinine, Quinidine, Atropine and Digitalis, *AM. HEART J.* 2:1, 1926.
14. Tobias, J. M., Lipton, M. A., and Lepinat, A. A.: Effect of Anesthetics and Convulsants on Brain Acetylcholine Content, *Proc. Soc. Exper. Biol. & Med.* 61:51, 1946.
15. Beattie, J., Brow, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus With Spinal Sympathetic Centres, *Proc. Roy. Soc., London, s. B* 106:253, 1930.
16. Brow, G. R., Long, C. N. H., and Beattie, J.: Irregularities of the Heart Under Chloroform, *J. A. M. A.* 95:715, 1930.
17. LeRoy, G. V., Fenn, G. K., and Gilbert, N. C.: The Influence of Xanthine Drugs and Atropine on the Mortality Rate After Experimental Occlusion of a Coronary Artery, *AM. HEART J.* 23:637, 1942.
18. Mintz, S. S., and Kondo, B.: The Effect of Atropine, Testosterone and Pitressin on Experimental Myocardial Infarction, *Proc. Soc. Exper. Biol. & Med.* 62:57, 1946.
19. Katz, L. N., and Jochim, K.: Observations on the Innervation of the Coronary Vessels of the Dog, *Am. J. Physiol.* 126:395, 1939.
20. Allen, C. R., Stutzman, J. W., Slocum, H. C., and Orth, O. S.: Protection From Cyclopropane-Epinephrine Tachycardia by Various Drugs, *Anesthesiology* 2:503, 1941.

LANATOSIDE C IN THE TREATMENT OF PERSISTENT PAROXYSMAL AURICULAR TACHYCARDIA

AUSTIN S. WEISBERGER, M.D., AND HAROLD FEIL, M.D.
CLEVELAND, OHIO

IN THE majority of cases, paroxysmal auricular tachycardia is a relatively benign disease. Attacks usually terminate spontaneously, or respond readily to reflex vagal stimulation such as carotid sinus pressure, ocular pressure, traction of the tongue, Valsalva's or Müller's experiments, induction of emesis, change of position, and so forth. There are, however, occasional attacks which are resistant to conservative measures and persist over a prolonged period of time. Prolongation of the rapid heart action may cause the patient marked apprehension and discomfort and may lead to cardiac failure, especially in the presence of underlying cardiac disease or other illness. Cooke and White¹ report seven cases in which death occurred and was either directly or indirectly attributable to paroxysmal supraventricular tachycardia. Vascular collapse, acute pulmonary edema, congestive failure, renal failure, embolic phenomena, and angina may occur.²⁻⁴ Central nervous system symptoms such as temporary blindness, vertigo, hemianopsia, blurring of vision, mental confusion, psychosis, convulsions, and coma have been reported.^{2,5} Levine⁶ states that hemiplegia and gangrene due to low pulse pressure and low cardiac output may result. Electrocardiograms simulating those of coronary thrombosis may be found after cessation of an attack of paroxysmal tachycardia.⁷ Rapid conversion of the abnormal mechanism is, therefore, desirable in many cases and may occasionally be life-saving.

A wide variety of drugs has been employed in the treatment of resistant paroxysmal auricular tachycardia. Mecholyl,^{8,9} prostigmine,¹⁰ physostigmine,¹¹ cinchona alkaloids,¹² cardiac glycosides,¹³ magnesium sulfate,¹⁴ calcium salts,¹⁵ potassium salts,¹⁶ metrazol,¹⁷ ergot derivatives, and parathyroid hormone⁶ have all been used successfully as therapeutic agents. Injection or surgical excision of the stellate ganglion^{18,19} has also been reported to be effective. Many of the drugs have undesirable side effects and toxic reactions. Some are not without considerable danger. Some are not very effective and others have been inadequately studied or are without rationale.

The choice of agent depends upon the urgency of the episode and the toxicity of the drug, but in general the least toxic drug that can be effective should be employed. Speed of action is desirable, but consistency in achieving the desired

From the Department of Medicine of Western Reserve University School of Medicine, and from Lakeside Hospital.

Received for publication March 21, 1947.

result, absence of undesirable side effects, and wide margin of safety are likewise important. Within recent years, rapidly acting crystalline digitalis preparations have been employed with increasing frequency and with frequent success. Junet²⁰ treated seven cases of paroxysmal auricular tachycardia with lanatoside C intravenously without a failure. Fahr and La Due²¹ treated five cases with the same preparation successfully. Schwab and Willis²² used *Digitalis lanata* and *Digitalis purpurea* preparations parenterally in seven cases with but one failure.

This report deals with further experience in the treatment of resistant paroxysmal auricular tachycardia with lanatoside C* intravenously.

CASE MATERIAL

Thirteen patients with prolonged refractory paroxysmal auricular tachycardia were treated with lanatoside C intravenously. One patient was treated with digalen intravenously. Seventeen paroxysms occurred in this group of cases. There were eight women and six men in the group and the ages ranged from 6 to 69 years. Complete data are given in Table I.

Ten of the fourteen patients had organic disease in addition to paroxysmal tachycardia. One patient was in Addisonian crisis with atypical pneumonia. Three patients had hypertensive cardiovascular disease and two of these had diabetes mellitus as well. One patient had arteriosclerotic heart disease and diabetes mellitus and one had tuberculous pericarditis. In one case the rapid heart action occurred during ligation of a patent ductus arteriosus, and in another it occurred after thyroidectomy (toxic adenoma). There was one case of intestinal obstruction and one of compression fracture of the spine. Three patients had cardiogenic shock and four patients were judged to be in early cardiac failure.

The diagnosis was confirmed electrocardiographically in all cases but one. Electrocardiograms, likewise, were taken during cessation of the attack in all cases but one. Patients with auricular flutter or paroxysmal auricular fibrillation were not included in this study. In all instances the attacks were of prolonged duration and did not respond to repeated and varied attempts at reflex vagal stimulation. Those found to be refractory were given 0.8 mg. (4.0 c.c.) of lanatoside C intravenously.† If no satisfactory response occurred within thirty minutes to an hour, another 0.8 mg. was given intravenously. No other medication was employed to control the tachycardia prior to, nor in conjunction with, the lanatoside C.

RESULTS

In sixteen cases the paroxysmal tachycardia ceased abruptly within forty minutes after the administration of the first dose of digitalis glycoside intravenously. One patient, who developed tachycardia during operation for the removal of a toxic adenoma of the thyroid, did not respond immediately but was found to have a normal mechanism approximately twelve hours after therapy (Case 10,

*Lanatoside C was furnished by Sandoz Chemical Works, Inc., New York, N. Y., under the trade name of Cedilanid.

†One patient, 6 years old, was given only 0.4 mg. of lanatoside C.

Table I). The time of response, excluding the case with delayed response, varied from four minutes to forty minutes and the average response was 17.6 minutes.

Ten patients responded to a dose of 0.8 mg. of lanatoside C, four patients to 1.6 mg., one patient to 1.0 mg., and one patient to 0.4 milligram. There were no toxic reactions nor undesirable side effects. The three instances of cardiogenic shock cleared up without further therapy.

Marked subjective and objective improvement occurred immediately in all cases upon cessation of the tachycardia. There was no immediate recurrence of the tachycardia. In those patients with organic disease the episode of tachycardia in no way affected the clinical course nor prolonged the hospital stay.

Five patients received carotid sinus pressure at varying intervals after the administration of the lanatoside C and in each case the paroxysm abruptly ceased, although repeated application of carotid sinus pressure previous to the injection of lanatoside C was ineffective. The remaining patients spontaneously reverted to a normal mechanism after therapy was instituted.

DISCUSSION

It is quite probable that the majority of these cases would have reverted to a normal mechanism without therapy. However, the desirability and necessity of rapid termination of the paroxysm in the patients is quite evident. It is entirely possible that the patient with Addisonian crisis, as well as those patients with underlying cardiovascular disease or cardiogenic shock, might have suffered serious complications or might have succumbed if the tachycardia had not been terminated rapidly. The alleviation of the patients' subjective distress was rapid and gratifying.

Carotid sinus pressure was ineffective prior to the institution of therapy in every case. However, five patients rapidly reverted to a normal mechanism when carotid sinus pressure was again attempted after lanatoside C was administered. Whether the response was due to the additive effect of the reflex vagal stimulation occurring with digitalization, or to increase in carotid sinus sensitivity, or to some other mechanism cannot be stated. It is possible that reapplication of carotid sinus pressure might have been successful without digitalis, but the uniform response in the face of previous failure makes this unlikely.

It is noteworthy that in this group of patients with resistant paroxysmal auricular tachycardia, ten of the fourteen, or 71.4 per cent, had associated organic disease. Marked delay in response occurred only in the patient with thyrotoxicosis. There was no correlation between the type and severity of the associated organic disease and the rapidity of response. The response of patients with uncomplicated paroxysmal tachycardia was no quicker than that of the remainder of the group.

Several patients with paroxysmal auricular flutter and paroxysmal auricular fibrillation were treated in an identical manner with lanatoside C while this series of cases was being collected. In these cases too, a rapid reduction in the ventricular rate occurred in every case and frequently a rapid reversion to normal

TABLE I. RESULTS OF LANATOSIDE C IN FOURTEEN PATIENTS WITH AURICULAR PAROXYSMAL TACHYCARDIA

CASE NO.	NAME	AGE	SEX	DIAGNOSIS	INITIAL HEART RATE	HEART RATE AFTER TREATMENT	MGM. LANATO-SIDE C	TIME OF RESPONSE
1	A. G. #142-067	36	M	Primary atypical pneumonia; Addisonian crisis; paroxysmal nodal tachycardia	155	108	0.8	10 min.
2	E. J. #234-601	24	M	Tuberculous pericarditis and myocarditis; paroxysmal auricular tachycardia	190	120	1.6	40 min.
3	M. L.	45	F	Paroxysmal auricular tachycardia	200	90	0.8	8 min.
4	I. D. #237-539	58	M	Intestinal obstruction; peritoneal abscess; paroxysmal auricular tachycardia	225	130	0.8*	12 min.
5	M. M. #164-047	36	F	Paroxysmal auricular tachycardia	180	84	0.8*	15 min.
				Paroxysmal auricular tachycardia	240	86	0.8*	9 min.
6	J. L. #246-711	6	M	Ligation of patent ductus arteriosus; paroxysmal auricular tachycardia during procedure	195	134	0.4	35 min.
7	B. S. #246-738	54	F	Compression fracture of spine; obesity; paroxysmal auricular tachycardia	160	98	1.6*	40 min.
8	H. S. #228-032	55	F	Hypertensive cardiovascular disease; diabetes mellitus; carcinomatosis; paroxysmal auricular tachycardia	214	94	0.8	5 min.

9	A. S. #140-657	66	F	Diabetes mellitus; arteriosclerotic heart disease; cardiac decompensation; shock; paroxysmal auricular tachycardia	187	97	0.8	4 min.
10	A. R. #254-094	46	F	Diabetes mellitus; arteriosclerotic heart disease; paroxysmal auricular tachycardia	217	88	0.8*	6 min.
11	E. M. #120-847	48	F	Toxic adenoma of the thyroid; paroxysmal auricular tachycardia, postoperatively	220	84	1.6	12 hours, approx.
12	J. S.	23	M	Paroxysmal auricular tachycardia	183	75	1.0	30 min.
13	E. S. #202-267	54	M	Paroxysmal auricular tachycardia	170	90	0.8	15 min.
				Hypertensive cardiovascular disease; diabetes mellitus; shock; paroxysmal auricular tachycardia with transient left bundle branch block	208	100	0.8	6 min.
				Same diagnosis as above; shock; paroxysmal auricular tachycardia (no bundle branch block)	140	96	1.6	36 min.
14	M. B. HC-4643	53	F	Hypertensive cardiovascular disease; paroxysmal nodal tachycardia	188	94	6.0 c.c. digalen	10 min.

*Carotid sinus pressure reapplied.

sinus rhythm was observed. These patients were not included in this group of cases.

The uniformity of response, the rapidity of action, and the absence of toxicity or undesirable side effects makes lanatoside C a valuable therapeutic agent in the treatment of paroxysmal auricular tachycardia which does not respond to reflex vagal stimulation. It should be re-emphasized that drug therapy need not be employed unless reflex vagal stimulation is unsuccessful.

SUMMARY AND CONCLUSIONS

1. Sixteen patients with persistent paroxysmal auricular tachycardia were treated with lanatoside C intravenously. One patient was treated with digalen intravenously.

2. In sixteen cases the paroxysmal tachycardia abruptly ceased within forty minutes. The average time of response in these fifteen cases was 17.6 minutes. In one case the response occurred within twelve hours.

3. No toxic reactions nor undesirable side effects occurred.

4. Lanatoside C is a safe and effective agent in the therapy of paroxysmal auricular tachycardia which does not respond to reflex vagal stimulation.

We wish to express our appreciation to Miss Marjorie Frasier for her technical assistance.

REFERENCES

1. Cooke, W. T., and White, P. D.: Prognosis in Paroxysmal Tachycardia and Paroxysmal Auricular fibrillation, *Brit. Heart J.* 4:153, 1942.
2. Wolff, Louis: Clinical Aspects of Paroxysmal Rapid Heart Action, *New England J. Med.* 226:640, 1942.
3. Wolff, L.: Cardinal Manifestations of Paroxysmal Tachycardia, Vascular Collapse, *New England J. Med.* 232:527, 1945.
4. Wolff, L.: Cardinal Manifestations of Paroxysmal Tachycardia, Anginal Pains, *New England J. Med.* 232:491, 1945.
5. Barnes, A. R.: Cerebral Manifestations of Paroxysmal Tachycardia, *Am. J. M. Sc.* 171: 489, 1926.
6. Levine, S.: Clinical Heart Disease, ed. 2, Philadelphia, 1940, W. B. Saunders Company.
7. Geiger, A. J.: Electrocardiograms Simulating Those of Coronary Thrombosis After Cessation of Paroxysmal Tachycardia, *AM. HEART J.* 26:555, 1943.
8. Starr, I., Jr.: Actyl-B-Methylcholine—Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, *Am. J. M. Sc.* 186:330, 1933.
9. Morgan, P. W.: Management of Paroxysmal Tachycardia Including Use of Mecholyl, *Ann. Int. Med.* 19:780, 1943.
10. Waldman, S., and Moskovitz, S. N.: Effect of Prostigmine on Supraventricular Tachycardias, Preliminary Report, *M. Rec.* 153:134, 1941.
11. Kaufman, R.: Ueber die Wirkung von Phyostigmin bei Tachykardie, *Wien. klin. Wchnschr.* 25:1080, 1912.
12. White, P. D.: Heart Disease, Ed. 3, New York, 1944, The Macmillan Company.
13. Wilson, F. N., and Wishart, S. W.: The Effect of Intravenous Administration of Digitalis in Paroxysmal Tachycardia of Supraventricular Origin, *AM. HEART J.* 5:549, 1930.
14. Boyd, L. J., and Scherf, D.: Magnesium Sulfate in Paroxysmal Tachycardia, *Am. J. M. Sc.* 206:43, 1943.
15. Wolfe, J. B., and Bellet, S.: Cessation of Attack of Auricular Paroxysmal Tachycardia by Use of Calcium, Preliminary Report, *Ann. Int. Med.* 4:795, 1931.
16. Stempfen, S. J., and Katz, Kermit: Quinidine and Potassium in the Treatment of Refractory Paroxysmal Ventricular Tachycardia, *AM. HEART J.* 24:555, 1942.

17. Boyd, W. W.: Metrazol in Auricular Paroxysmal Tachycardia, *J. South Carolina M. A.* 38:317, 1942.
18. Coleman, E. P., and Bennett, D. A.: Injection of Right Stellate Ganglion With Alcohol in Paroxysmal Tachycardia, *Surg., Gynec. & Obst.* 67:349, 1938.
19. Le Riche: Considerations sur la possibilité d'un traitement chirurgical de la tachycardie paroxystique, *Lyon chir.* 21:39, 1924.
20. Junet, R.: La therapeutique de la tachycardia paroxystique. A propos de quelques cas traites par las digitale laineuse, *Rev. méd. de la Suisse Rom.* 60:13, 1940.
21. Fahr, G., and LaDue, J.: A Preliminary Investigation of the Therapeutic Value of Lanatoside C. (Digilanid C.), *AM. HEART J.* 21:133, 1941.
22. Schwab, E. H., and Willis, J. G.: Paroxysmal Tachycardia of Supraventricular Origin, *South. M. J.* 35:687, 1942.

AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

V. THE EFFECT OF CHANGING HEART RATE UPON THE Q-T INTERVAL AND THE T-P INTERVAL AND THEIR RESPECTIVE RELATIONSHIPS TO THE CYCLE LENGTH (R-R INTERVAL)

ISADORE SCHLAMOWITZ, M.D.
NEW YORK, N.Y.

OF INTEREST to many investigators has been the question of determining exactly what happens to the Q-T interval, the T-P interval, and the cycle length (C) as measured in the electrocardiogram while the heart rate is changing. Lombard and Cope,¹ measuring systole and diastole by mechanical means, found that diastole shortened more rapidly than systole with increase in heart rate. Bazett² found that the ratio $K = \frac{Q-T}{\sqrt{C}}$ was temporarily increased immediately after exercise. White and Mudd³ found that the Q-T to C relationship was not altered after exercise. Blair, Wedd, and Young⁴ noted that immediately after exercise the Q-T and C were shorter than before exercise and that, as the C returned to the resting level, the Q-T lengthened, although at a slower rate, until it too had reached the resting level. However, the Q-T continued for a time to lengthen beyond that level while C remained constant. White, Kossmann, and Ershler⁵ in their study found that the ratio $\frac{Q-T}{\sqrt{C}}$ became smaller immediately after exercise. In two previous reports^{6,7} it was shown that the Q-T to C and T-P to C relationships [$K(Q-T)$ and $K(T-P)$] were not disturbed immediately after exercise, but no information was available as to what happened while the heart rate was changing. It was for the purpose of obtaining information about this phase that this study was undertaken.

METHOD

The procedure followed was the same as that outlined in the study reported previously⁸ with the following modifications. Only fifty-two of the fifty-three normal young men were retained for this study. Electrocardiograms were taken while the subject was seated in a comfortable straight-backed chair with his right foot resting on a pedal. The pedal was a board attached to the floor at one

From the Department of Therapeutics, New York University College of Medicine.
Received for publication Jan. 22, 1947

end by hinges and to a weight by means of rope and pulley at the other end. Stops were so placed that the distal (weighted) end of the board could traverse a distance of about six inches. The work performed in lifting the weight with the pedal was enough to induce a tachycardia. Thus, we were able to record the electrocardiograms during exercise. In each case the three standard limb leads were recorded at rest after the heart rate had become stabilized. Then, Lead II was recorded during ten of every fifteen seconds, or, in some cases, continuously while the subject exercised. When a tachycardia had been produced, exercise was stopped and tracings (Lead II) continued to be recorded until the heart rate had returned to the resting level and remained there for two minutes. In each individual the cycle length, Q-T interval, and T-P interval were measured and recorded for the different heart rates. The criteria used in selecting and measuring the cycles and intervals have been outlined previously.⁶⁻⁸ Table I shows the age distribution of the fifty-two subjects retained for this study.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YR.)	NUMBER
19	2
20	5
21	12
22	17
23	11
24	3
25	0
26	1
27	0
28	0
29	0
30	1
Total	52

RESULTS AND DISCUSSION

In analyzing the data, it was found that the period from the beginning to the completion of the experiment in each instance could be divided into three stages as follows: (1) the stage during which the heart rate increases (cycle length becomes shorter), (2) the stage when the heart rate decreases (cycle length lengthens), and (3) the stage at which the heart rate has returned to the control level. Since the rates of change of the heart rate (and cycle length) and Q-T and T-P intervals vary so much from individual to individual, it was found to be impractical to draw a composite set of curves for the entire group. Therefore, only a few characteristic curves are illustrated in Fig. 1.

Examination of the curves reveals that during the first stage the K(Q-T) values become larger with shortening of the cycle length. During the second stage the K(Q-T) values become smaller than the control values. Finally, the K(Q-T) values reach a level that is the same as or close to the pre-exercise levels when the cycle length has returned to its resting level. At one point between

the first and second stages the $K(Q-T)$ values are the same as those of the pre-exercise period. To help analyze the data further, the largest $K(Q-T)$ value ["peak" $K(Q-T)$], as well as the mean of all the $K(Q-T)$ values ["mean" $K(Q-T)$] during the first stage, was determined in each case (Table II). The mean of the "peak" $K(Q-T)$ and the mean of the "mean" $K(Q-T)$ were determined, and their deviations from the mean of the control $K(Q-T)$ values were tested for

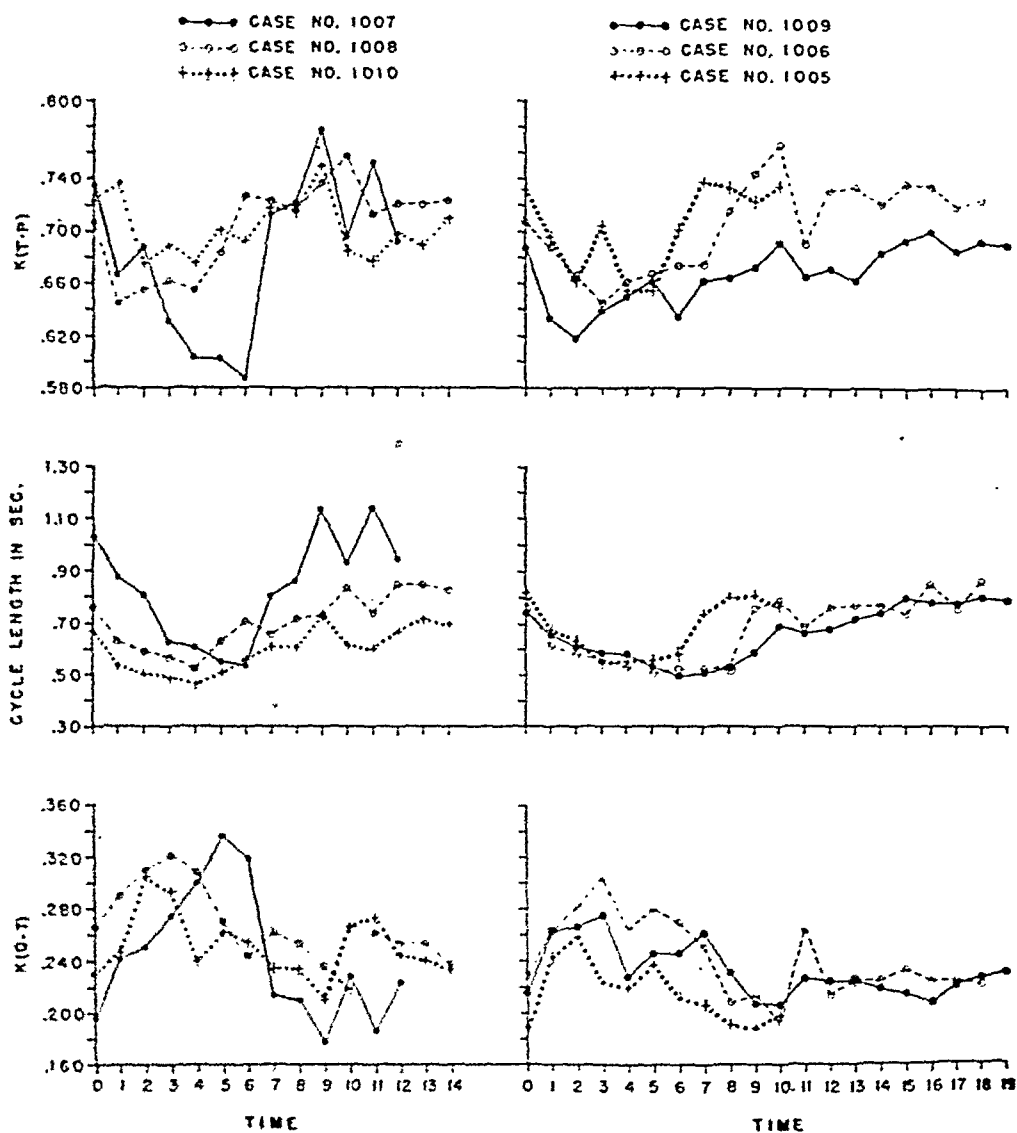


Fig. 1.—The effect of changing cycle length on $K(Q-T)$ and $K(T-P)$ as illustrated in six normal young men.

significance. It was found that the mean of the control $K(Q-T)$ values was 0.237, with a standard deviation of ± 0.021 . The mean of the "peak" $K(Q-T)$ was 0.293, with a standard deviation of ± 0.029 . The t value for the difference between the mean of the control $K(Q-T)$ and the mean of the "peak" $K(Q-T)$ was found to be 11.436. The t value for the difference between the mean of the control $K(Q-T)$ and the mean of the "mean" $K(Q-T)$ was found to be 7.734.

TABLE II. PEAK AND MEAN VALUES FOR K(Q-T) DURING PERIOD OF INCREASING HEART RATE

NO.	CASE	CONTROL K(Q-T)	PEAK K(Q-T)	MEAN K(Q-T)
1	1002	.230	.309	.284
2	1003	.246	.273	.255
3	1004	.281	.295	.287
4	1005	.190	.259	.242
5	1006	.230	.304	.279
6	1007	.197	.327	.286
7	1008	.267	.321	.307
8	1009	.219	.276	.254
9	1010	.230	.306	.271
10	1011	.219	.289	.252
11	1012	.249	.296	.263
12	1013	.251	.296	.271
13	1014	.262	.290	.266
14	1015	.187	.270	.252
15	1016	.220	.277	.273
16	1017	.285	.346	.258
17	1018	.231	.308	.292
18	1020	.221	.302	.268
19	1021	.247	.320	.281
20	1022	.222	.296	.276
21	1023	.250	.333	.291
22	1024	.224	.243	.243
23	1025	.236	.264	.217
24	1026	.233	.260	.228
25	1027	.254	.284	.277
26	1028	.209	.294	.263
27	1029	.233	.240	.232
28	1030	.241	.327	.302
29	1031	.204	.212	.211
30	1032	.256	.281	.281
31	1033	.244	.284	.267
32	1034	.229	.291	.259
33	1035	.270	.271	.271
34	1036	.216	.258	.257
35	1037	.263	.273	.246
36	1038	.245	.327	.321
37	1039	.241	.286	.283
38	1040	.261	.333	.295
39	1041	.235	.323	.282
40	1042	.262	.298	.292
41	1044	.244	.259	.240
42	1045	.247	.267	.237
43	1047	.245	.292	.275
44	1048	.221	.266	.259
45	1049	.250	.333	.280
46	1050	.217	.300	.267
47	1051	.213	.323	.294
48	1052	.240	.355	.289
49	1053	.245	.318	.298
50	1054	.248	.273	.265
51	1055	.228	.306	.302
52	1056	.244	.278	.278
Mean K(Q-T)		0.237	0.293	0.270
Standard deviation		± 0.021	± 0.029	± 0.023

Comparison of "Peak" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.004897$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.056}{0.004897} = 11.436$$

 \bar{X}_1 = Mean of "peak" K(Q-T)

 \bar{X}_2 = Mean of control K(Q-T)
Comparison of "Mean" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.004267$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.033}{0.004267} = 7.734$$

 \bar{X}_1 = Mean of "mean" K(Q-T)

 \bar{X}_2 = Mean of control (K(Q-T))

Thus, it is seen that the deviations of K(Q-T) which occur during the first stage are highly significant. The second stage was analyzed similarly (Table III). The difference between the mean of the "mean" K(Q-T) and the mean of the control K(Q-T) was found to be not statistically significant. However, the mean of the "peak" K(Q-T) differed from the mean of the control K(Q-T) significantly. It is therefore seen that the K(Q-T) value becomes significantly greater during the first stage, whereas during the second stage only isolated readings of K(Q-T) are significantly smaller than the K(Q-T) value during the control period. From this data and from perusal of the individual Q-T and C values in each case it is seen that the rate of change of the Q-T interval lags slightly behind the rate of change of the cycle length during changing heart rate. However, the direction of change is the same for both.

In Fig. 1 it is seen that with the shortening of the cycle length the value of K(T-P) becomes smaller during the first stage. During the second stage the value of K(T-P) becomes greater and surpasses the control value. Finally, K(T-P) assumes the control value during the third stage. At one point between the first and second stages the value of K(T-P) is the same as that of the pre-exercise period. In Table IV are listed the "peak" K(T-P) (that is, the smallest value of K(T-P) during the first stage), as well as the "mean" K(T-P) (that is, the mean of all K(T-P) values during the first stage), for each subject. Upon determining their respective means and testing the significance of their deviations from the mean of the control K(T-P), it is seen that the difference between the mean of the "peak" K(T-P) and the mean of the control K(T-P), as well as the difference of the mean of the "mean" K(T-P) from the mean of the control K(T-P), is statistically significant. The data obtained during the second stage was similarly analyzed and, as is seen in Table V, only the difference between the mean of the "peak" K(T-P) and mean of the control K(T-P) was statistically significant. The mean of the "mean" K(T-P) did not differ significantly from the control value. It is seen, therefore, that during the first stage there is a significant de-

TABLE III. PEAK AND MEAN VALUES FOR K(Q-T) DURING PERIOD OF DECREASING HEART RATE

NO.	CASE	PEAK K(Q-T)	MEAN K(Q-T)
1	1002	.211	.244
2	1003	.226	.245
3	1004	.236	.257
4	1005	.207	.219
5	1006	.194	.231
6	1007	.178	.201
7	1008	.218	.248
8	1009	.207	.227
9	1010	.210	.239
10	1011	.202	.216
11	1012	.206	.243
12	1013	.214	.248
13	1014	.220	.235
14	1015	.178	.215
15	1016	.199	.224
16	1017	.279	.305
17	1018	.213	.241
18	1020	.196	.222
19	1021	.177	.228
20	1022	.208	.234
21	1023	.222	.261
22	1024	.208	.224
23	1025	.208	.254
24	1026	.199	.226
25	1027	.217	.253
26	1028	.199	.229
27	1029	.225	.232
28	1030	.218	.268
29	1031	.203	.207
30	1032	.191	.259
31	1033	.214	.244
32	1034	.212	.213
33	1035	.220	.254
34	1036	.197	.229
35	1037	.217	.242
36	1038	.235	.257
37	1039	.244	.258
38	1040	.240	.271
39	1041	.196	.224
40	1042	.197	.233
41	1044	.209	.248
42	1045	.181	.218
43	1047	.203	.240
44	1048	.181	.208
45	1049	.218	.249
46	1050	.176	.203
47	1051	.237	.271
48	1052	.179	.229
49	1053	.199	.236
50	1054	.238	.254
51	1055	.205	.246
52	1056	.204	.216
Mean K(Q-T)		0.209	0.238
Standard deviation		± 0.020	± 0.020

Comparison of "Peak" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.003966$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.028}{0.003966} = 7.060$$

\bar{X}_1 = Mean of control K(Q-T)

\bar{X}_2 = Mean of "peak" K(Q-T)

Comparison of "Mean" K(Q-T) With Control K(Q-T)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00398$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.001}{0.00398} = 0.252$$

\bar{X}_1 = Mean of "mean" K(Q-T)

\bar{X}_2 = Mean of control K(Q-T)

crease in the value of K(T-P), whereas during the second stage only isolated readings may be significantly greater than the control K(T-P). These data plus a perusal of the individual T-P and C values in each case show that, although the direction of change is the same in both C and T-P, the rate of change in T-P is greater than the rate of change in the cycle length.

On the basis of this work it is felt that a constant relationship between Q-T and C and between T-P and C holds in normal young men only when the heart rate is stable. Whenever this stability is upset and the heart rate is changing, the relationships are disturbed. In two previous reports^{6,7} it was shown that the relationships K(Q-T) and K(T-P) were not disturbed immediately after exercise. In reviewing this previous data and method in the light of our present experience it is felt that the reason no disturbance of the K(Q-T) and K(T-P) relationships was found immediately after exercise was that practically all of the afterexercise tracings were recorded during the short transition period between the first and second stages when the K(Q-T) and K(T-P) values are practically the same as those of the pre-exercise period. It is conceivable that a slight delay in recording the afterexercise tracings might have placed us in the middle of the second stage; but, even if all of the after exercise tracings had been recorded during the second stage, our conclusion might have been the same, for, as was shown in the foregoing, the deviations of the means of all the "mean" K(Q-T) and the "mean" K(T-P) from their respective control means are not statistically significant. It is only the extreme K(Q-T) and K(T-P) values that deviate significantly, and unless continuous tracings were taken, the likelihood is that the scatter of the K(Q-T) and K(T-P) values for the entire group would be such as to give us a set of means that did not deviate significantly from the control values.

TABLE IV. PEAK AND MEAN VALUES FOR K (T-P) DURING PERIOD OF INCREASING HEART RATE

NO.	CASE	CONTROL K(T-P)	PEAK K(T-P)	MEAN K(T-P)
1	1002	.687	.566	.609
2	1003	.644	.630	.657
3	1004	.660	.640	.657
4	1005	.732	.662	.688
5	1006	.708	.644	.666
6	1007	.735	.587	.629
7	1008	.707	.646	.655
8	1009	.686	.618	.639
9	1010	.722	.674	.693
10	1011	.694	.598	.657
11	1012	.672	.613	.676
12	1013	.622	.576	.595
13	1014	.671	.639	.654
14	1015	.714	.667	.686
15	1016	.728	.662	.667
16	1017	.685	.634	.723
17	1018	.690	.612	.617
18	1020	.714	.661	.677
19	1021	.712	.643	.668
20	1022	.720	.631	.653
21	1023	.661	.578	.626
22	1024	.711	.678	.678
23	1025	.699	.684	.722
24	1026	.678	.685	.705
25	1027	.694	.662	.680
26	1028	.688	.566	.605
27	1029	.657	.660	.686
28	1030	.691	.622	.659
29	1031	.748	.723	.732
30	1032	.688	.702	.702
31	1033	.680	.657	.673
32	1034	.706	.620	.657
33	1035	.683	.688	.688
34	1036	.728	.667	.670
35	1037	.675	.660	.674
36	1038	.691	.605	.609
37	1039	.679	.624	.630
38	1040	.671	.584	.633
39	1041	.666	.561	.597
40	1042	.682	.616	.644
41	1044	.646	.614	.672
42	1045	.681	.667	.708
43	1047	.683	.612	.638
44	1048	.700	.651	.662
45	1049	.691	.589	.643
46	1050	.716	.643	.659
47	1051	.731	.590	.627
48	1052	.770	.544	.633
49	1053	.686	.616	.633
50	1054	.713	.681	.693
51	1055	.721	.612	.626
52	1056	.692	.649	.649
Mean K(T-P)		0.694	0.633	0.659
Standard deviation		± 0.027	± 0.039	± 0.032

Comparison of "Peak" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00662$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.061}{0.00662} = 9.215$$

\bar{X}_1 = Mean of control K(T-P)

\bar{X}_2 = Mean of "peak" K(T-P)

Comparison of "Mean" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00587$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.035}{0.00587} = 5.963$$

\bar{X}_1 = Mean of control K(T-P)

\bar{X}_2 = Mean of "mean" K(T-P)

Since changing heart rate disturbs the K(Q-T) and K(T-P) ratios, it is important to note whether or not the heart rate was stable in all instances where these relationships or even where only the Q-T interval is being studied. Unless the heart rate was known to be stable at the time the tracings were recorded there is no basis for comparing the values for K(Q-T), K(T-P), or Q-T with the "normal" or "control" values. This is especially true in acute experiments where the heart rate is disturbed by such factors, for example, as induced anoxia, hyperthermia, effects of short-acting drugs such as epinephrine, etc., and emotional factors. This must also be kept in mind when studying the tracings of young individuals, for sinus arrhythmia is a common finding among these persons.

CONCLUSIONS

1. In normal young men the Q-T interval to cycle length relationship is disturbed during changing heart rate produced by exercise. The K(Q-T) becomes larger during the period of increasing heart rate and hovers around the control level with wide fluctuations toward smaller values during the period of decreasing heart rate. This is due to the fact that the rate of change of Q-T is slower than the rate of change of the cycle length.

2. In normal young men the T-P interval to cycle length relationship is disturbed during changing heart rate produced by exercise. The K(T-P) becomes smaller during the period of increasing heart rate and hovers around the control level with wide fluctuations toward larger values during the period of decreasing heart rate. This is due to the fact that the rate of change of T-P is greater than the rate of change of the cycle length.

TABLE V. PEAK AND MEAN VALUES FOR K(T-P) DURING PERIOD OF DECREASING HEART RATE.

NO.	CASE.	PEAK K(T-P)	MEAN K(T-P)
1	1002	.718	.669
2	1003	.690	.673
3	1004	.706	.697
4	1005	.739	.688
5	1006	.768	.715
6	1007	.778	.737
7	1008	.758	.724
8	1009	.691	.670
9	1010	.749	.714
10	1011	.708	.689
11	1012	.746	.698
12	1013	.641	.616
13	1014	.704	.692
14	1015	.780	.729
15	1016	.758	.727
16	1017	.705	.677
17	1018	.729	.694
18	1020	.742	.714
19	1021	.799	.735
20	1022	.739	.697
21	1023	.706	.657
22	1024	.723	.702
23	1025	.735	.679
24	1026	.760	.726
25	1027	.727	.687
26	1028	.704	.663
27	1029	.690	.677
28	1030	.667	.660
29	1031	.749	.732
30	1032	.778	.691
31	1033	.741	.700
32	1034	.736	.727
33	1035	.712	.689
34	1036	.747	.707
35	1037	.712	.696
36	1038	.701	.682
37	1039	.692	.671
38	1040	.704	.667
39	1041	.717	.675
40	1042	.771	.720
41	1044	.696	.663
42	1045	.767	.733
43	1047	.763	.705
44	1048	.716	.708
45	1049	.732	.685
46	1050	.766	.727
47	1051	.708	.658
48	1052	.756	.691
49	1053	.758	.709
50	1054	.709	.685
51	1055	.744	.694
52	1056	.729	.715
Mean K(T-P)		0.730	0.695
Standard deviation		± 0.031	± 0.025

Comparison of "Peak" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00579$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.036}{0.00579} = 6.218$$

\bar{X}_1 = mean of peak K(T-P)

\bar{X}_2 = Mean of control K(T-P)

Comparison of "Mean" K(T-P) With Control K(T-P)

$$sd = \sqrt{\frac{V}{N_1} + \frac{V}{N_2}}$$

$$sd = 0.00516$$

$$t = \frac{\bar{X}_1 - \bar{X}_2}{sd} = \frac{0.001}{0.00516} = 0.194$$

\bar{X}_1 = Mean of "mean" K(T-P)

\bar{X}_2 = Mean of control K(T-P)

3. The importance of these disturbances in the K(Q-T) and K(T-P) ratios and their influence in certain circumstances are discussed.

The author wishes to thank Dr. Arthur C. DeGraff, Professor of Therapeutics at New York University College of Medicine, for having made this study possible and for his helpful suggestions.

REFERENCES

1. Lombard, W. P., and Cope, O. M.: Effect of the Pulse Rate on the Length of the Systoles and Diastoles of the Normal Human Heart in the Standing Position, *Am. J. Physiol.* 49:139, 1919.
2. Bazett, H. C.: An Analysis of the Time Relations of Electrocardiograms, *Heart* 7:353, 1920.
3. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7:387, 1929.
4. Blair, H. A., Wedd, A. M., and Young, A. C.: The Relation of the Q-T Interval to the Refractory Period, the Diastolic Interval, the Duration of Contraction, and the Rate of Beating in Heart Muscle, *Am. J. Physiol.* 132:157, 1941.
5. White, M. S., Kossmann, C. E., and Ershler, I.: The Effect of High Altitude and Rebreathing on the Duration of Electrical Systole in Man, *AM. HEART J.* 24:230, 1942.
6. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. I. The Duration of the Q-T Interval and Its Relationship to the Cycle Length (R-R Interval), *AM. HEART J.* 31:329, 1946.
7. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. II. The Duration of the T-P Interval and Its Relationship to the Cycle Length (R-R Interval), *AM. HEART J.* 31:464, 1946.
8. Schlamowitz, I.: An Analysis of the Time Relationships Within the Cardiac Cycle in Electrocardiograms of Normal Men. IV. The Effect of Position Change on the Relationship of the Q-T and the T-P Interval Respectively to the Cycle Length (R-R Interval), *AM. HEART J.* 31:702, 1947.
9. Snedecor, G. W.: Statistical Methods, ed. 3, Ames, 1940, The Iowa State College Press.

Clinical Reports

PAROXYSMAL DIAPHRAGMATIC FLUTTER WITH SYMPTOMS SUGGESTING CORONARY THROMBOSIS

FERRALL H. MOORE, M.D., REDWOOD CITY, CALIF., AND
CHARLES SCHOFF, M.D., SAN FRANCISCO, CALIF.

FROM time to time, since 1936, reports have appeared in the literature concerning a nomadic individual of various aliases, who presents the unusual association of recurring attacks of diaphragmatic flutter, symptoms suggestive of coronary thrombosis, and psychopathic prevarication. Porter¹ of Virginia first described the temporary relief of severe anginal pain in this patient by procaine infiltration of each phrenic nerve, after kymography and fluoroscopy had revealed the presence of diaphragmatic flutter. In his description of the syndrome he concluded that the term "cardiodiaphragmatic angina" was justified. In 1939, Whitehead and associates² of Colorado University published extensive observations on the same patient; during his hospital stay a left phrenicotomy and a right phrenic crush were done to arrest the episode of diaphragmatic flutter, with evident temporary success and relief of precordial pain. An additional communication concerning this individual was included in the same article, in the form of observations by Lagen and others at the University of California Hospital on this patient a year later. At that time, left phrenic exeresis (31 cm.) and right phrenicotomy were done by the California group with relief of the flutter episode and of the anginal pain. During this latter period of observation evidence of hysterical or feigned hemiplegia were recorded; frequently elevated temperature was thought due to malingering. In 1941, Goodman³ of Oregon University reported temporary relief of anginal pain and flutter of the diaphragm in the same man by ethyl chloride refrigeration over the phrenics, and suggested this procedure for further trial in other forms of disturbed diaphragmatic motility. The last communication concerning the patient was submitted by Caine and Ware,⁴ who in 1944 treated him in an Army hospital for the same condition, the paroxysms of flutter, pain, and dyspnea finally ceasing after treatment with bed rest, morphine, and oxygen. In addition to the published reports just cited, it is known that this same patient has been seen and treated for his fluttering diaphragm and angina in at least six other institutions, mostly on the Pacific coast. In each instance house staffs have been intrigued

by the various callings and pursuits alleged by the subject, and the saga of his life as related in various hospitals has revealed him as a deep sea diver, a miner, trapper, sheriff, and retired Army officer. In nearly all instances, evidences of psychopathy also have included malingering or belligerency. Identification has been possible by means of pictures, scars, and tatoo marks, as well as by means of the association of complaints. The observations here submitted confirm previous ones, and attempt to add further to the clinical picture of the attack as seen.

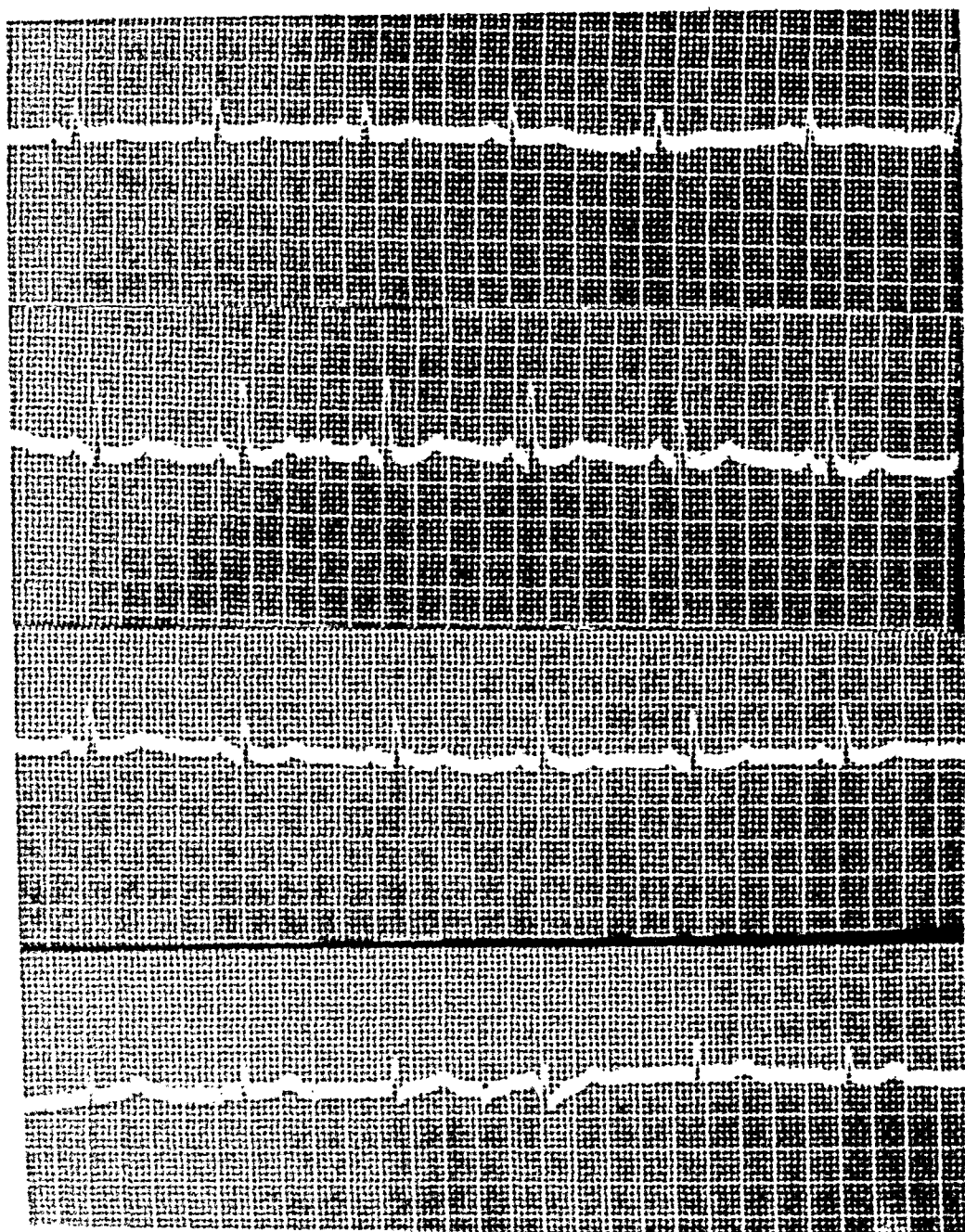


FIG. 1.—Electrocardiogram taken during the height of a paroxysm of diaphragmatic flutter.

CASE REPORT

On Aug. 14, 1946, a man was brought by the police to the emergency room of Palo Alto Hospital, stating that he had been seized by severe chest pain and had collapsed while getting off a bus. He gave the name of "Lewis Allen", was dressed in khaki enlisted men's clothing and Army garrison cap, and complained bitterly of agonizing precordial pain, clutching his left breast, moaning, and gritting his teeth. Examination revealed a thin, undernourished man around 60 years of age, with thin gray-brown hair; the eyes were light brown, with small but normally reacting pupils. Marked septal deviation occluded the right nostril, and complete dentures were present. A diagonal white scar traversed the central portion of the lower lip. On each side of the neck old transverse scars 5 cm. in length were present a short distance above the clavicle, just lateral to the sternomastoid insertions. An eagle was tattooed on the right forearm, and a wreath of flowers on the left. On auscultation over the precordium a loud rapid booming sound was heard, about 240 per minute in frequency, in the presence of a pulse rate of 72 at the wrist. Palpation over the lower thorax both back and front, conveyed a marked throbbing sensation to the hand synchronous with the sounds described. The blood pressure was 90/60. Physical examination was otherwise not remarkable.

Because of the bitter complaints of "pain in my heart" a tentative diagnosis of coronary thrombosis was made, and morphine sulphate, $\frac{1}{4}$ grain, was given hypodermically. Following this, an electrocardiogram was run (Fig. 1) which revealed a sinus rhythm with a rate of 70, and no changes suggestive of either coronary insufficiency or of infarction. At this juncture, the similarity existing between the patient and the one described in the literature occurred to us, and he was placed under the fluoroscope. Here both leaves of the diaphragm were seen to be fluttering rapidly in time with the palpable impulses and audible sounds previously noted. The excursion of the leaves was estimated as between 5 and 10 mm., and seemed slightly more marked on the right side. The left leaf of the diaphragm was elevated to the level of the fifth rib, with slight shift of the cardiac shadow to the right (Fig. 2).

The patient continued to cry out with distress and evince all signs of severe pain despite the hypodermically administered morphine. A second dose of $\frac{1}{8}$ grain was given, this time by vein, slowly, and with relief of pain. The flutter, however, was not stopped, but was noted to assume a more irregular rhythm at a somewhat slower rate, disappearing spontaneously several hours later not to recur. A routine complete blood count was within normal limits, and the Kolmer was negative. A six-foot roentgenogram of the chest (Fig. 2) merely confirmed previous fluoroscopic observations of cardiophrenic relations. A recheck electrocardiogram on the following day failed to show any interim changes.

On further conversation with the patient, he stated that he was a retired Navy ensign, recently released from Santo Tomas internment camp in the Philippines, where he stated that he had been imprisoned by the Japanese since 1941. The scar on his lower lip, he explained, was due to a Japanese sniper's bullet, and the scars at the base of his neck were due to old operations "for tuberculosis." He also stated that he had served as a "radar installer" in the amphibious assaults on Tarawa, Saipan, Iwo Jima, and Okinawa, which seem to constitute a temporal paradox worthy of note. On being questioned as to previous attacks of chest pain or flutter of the diaphragm, and previous hospital admissions, he denied any such incidents but was quick to refuse us permission to photograph him. The next day after admission he stated that he felt fine and desired to go to a nearby city for his pension check. This he was allowed to do, since the need of hospital beds was urgent at the time.

COMMENT

In view of the extensive phrenic interruptions carried out on this man, particularly in regard to the left nerve and left leaf of the diaphragm, it is felt that the episodes of flutter may at present be due either to the presence of accessory phrenic pathways, or to a myogenic tic of the diaphragm.

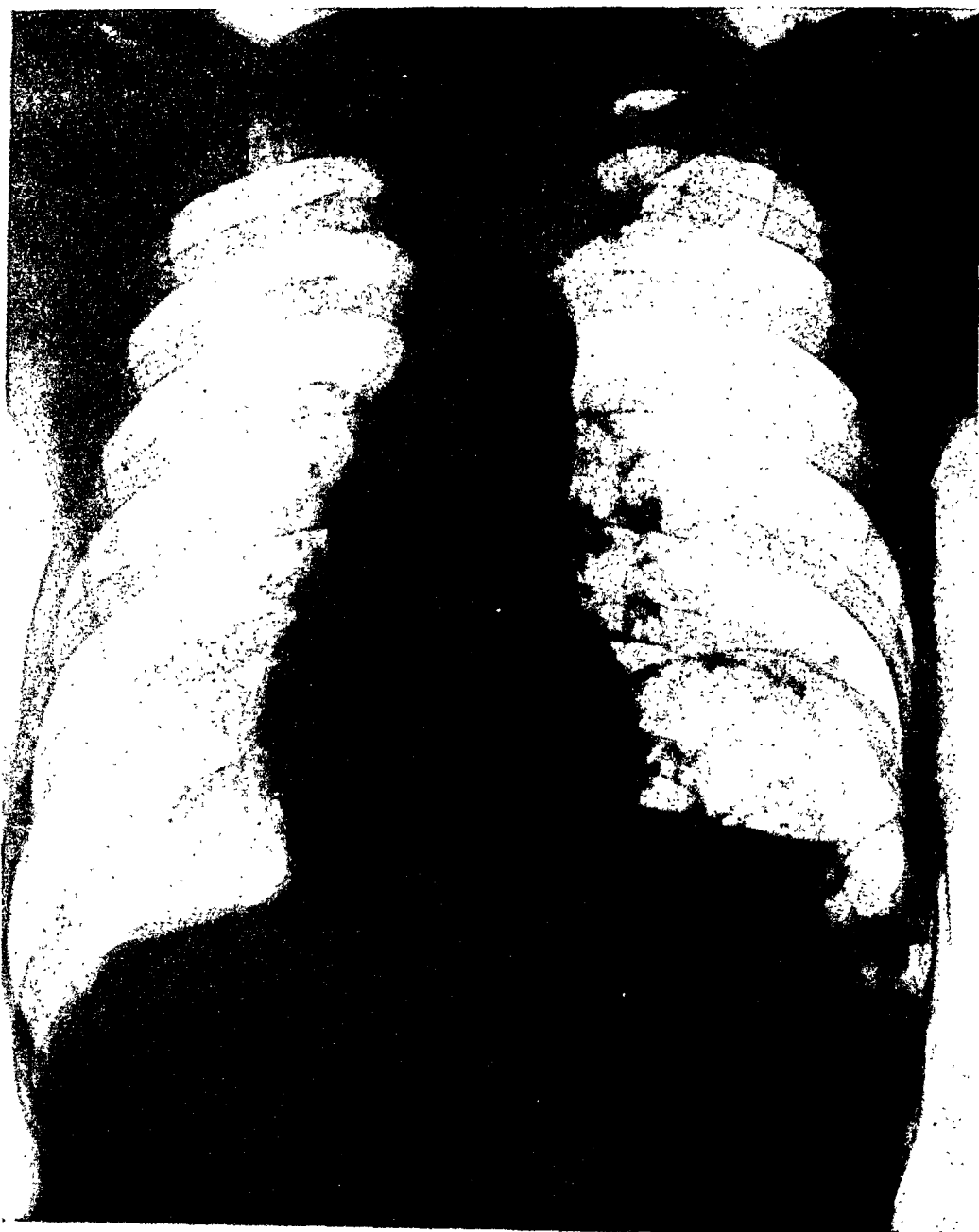


Fig. 2.—Teleroentgenogram made the day after the termination of a paroxysm of diaphragmatic flutter.

Exclusive of electrocardiographic and fluoroscopic findings, certain features of the clinical picture presented here have offered bedside evidence arguing against a diagnosis of acute coronary accident, should this same individual be encountered by the reader. Foremost was the absence of pain across the upper chest, and the alleged radiation of pain from the region of the cardiac apex into the left arm. Of almost equal significance was the behavior during the attack, the patient moving about more actively with his hysterics than does the usual victim relatively immobilized by angina. Finally, it is unlikely that an examiner palpating the throb, or hearing the loud bruit of

the rapidly contracting diaphragm, would associate the complaints with the heart for long in the presence of a normal pulse rate. This man will no doubt make more appearances in various hospitals throughout the country, and it is hoped that these observations, along with those previously published, may enable others more readily to arrive at a correct diagnosis. The possibility of diaphragmatic flutter may be called to mind in unusual types of paroxysmal precordial pain.

SUMMARY

Further observations are submitted concerning an individual who presents the syndrome of associated diaphragmatic flutter and pain suggestive of acute coronary insufficiency. Practical differential diagnostic suggestions are made for bedside diagnosis.

REFERENCES

1. Porter, W. B.: Diaphragmatic Flutter With Symptoms of Angina Pectoris, *J. A. M. A.* 106:992, 1936.
2. Whitehead, R. W., Burnett, C. T., and Lagen, J. B.: Diaphragmatic Flutter With Symptoms Suggesting Angina Pectoris, *J. A. M. A.* 112:1237, 1939.
3. Goodman, Morton J.: Paroxysmal Flutter of the Diaphragm Simulating Coronary Occlusion; Further Observations of an Extraordinary Case Controlled by Refrigeration of the Phrenic Nerve, *J. A. M. A.* 116:1635, 1941.
4. Cain, Edmund F., and Ware, E. Richmond: Diaphragmatic Flutter, *J. A. M. A.* 131:1058, 1946.

DOUBLE RUPTURE OF THE HEART FOLLOWING MYOCARDIAL INFARCTION

REPORT OF A CASE

DOUGLAS CARROLL, M.D., AND SAMUEL D. CUMMINS, M.D.
BALTIMORE, MD.

AN UNCOMMON complication of myocardial infarction is rupture of the interventricular septum. A subsequent rupture of the ventricular wall is evidently unusual, for a fairly wide search of the literature reveals no report of such a case.

CASE REPORT

A 60-year-old Merchant Marine carpenter entered the hospital on Jan. 21, 1946, complaining of shortness of breath of one week's duration. He had felt perfectly well until one week before admission to the hospital when, early in the afternoon, he noted a "burning" sensation in the epigastrium. His duties were light, and he had not overexerted himself at any time. He rested in the afternoon, and the sensation of burning passed away. On the following day he experienced mild orthopnea and dyspnea, both of which were ingravescent until admission. Four days later there was a recurrence of the epigastric burning, associated with radiation of mild pain from the epigastrium to the right side of the neck and down the right arm, which lasted several hours. Because of the increasing difficulty in breathing, he reported to the hospital.

He gave no past history of hypertension, but his blood pressure had not been taken for several years.

On physical examination, he was found sitting on the side of the bed, moderately cyanotic, extremely dyspneic, and perspiring freely. The rectal temperature was 98.0° Fahrenheit. The pulse rate was 100, and the respirations were 20 per minute. The blood pressure was 105/90. The heart was believed to be enlarged to the left, but the exact degree of enlargement could not be estimated accurately because the chest wall was thick. There was no thrill. There was a presystolic gallop rhythm, heard best over the aortic area. The heart sounds were normal. There was an extremely loud systolic murmur heard at the apex and transmitted over the precordium and the left upper quadrant of the abdomen. Examination of the lungs revealed the presence of medium moist râles over the lower two-thirds of the lungs. The liver was not palpable. There was no ascites. There was minimal ankle edema.

The white blood count showed 16,250 leucocytes, with a differential count of 86 per cent segmented cells and 14 per cent lymphocytes. Urinalysis was negative. The sedimentation was 3 mm. in one hour. A portable chest plate was reported as showing enlargement of the heart to the left with mottling in the lower lung fields, compatible with pulmonary edema. An electrocardiogram showed a Q-T₂ type of ventricular complex, characteristic of posterior myocardial infarction.

He was placed on complete bed rest and given oxygen continuously by mask. On the second and third days of hospitalization, he had a temperature of 102.0° F. rectally in the late afternoon.

From the Johns Hopkins Hospital, Baltimore.
Received for publication Nov. 23, 1946

Because of the signs of severe cardiac failure, he was given digitalis orally. He received 0.3 Gm. three times a day on the first day and on the second day, 0.2 Gm. three times a day. Thereafter he received 0.1 Gm. daily. The gallop rhythm disappeared on the second day, and his dyspnea and orthopnea decreased. For the first two days his fluids were limited to 1,000 c.c. of liquid, and he was given a low-salt diet. Morphine was occasionally used at night for the relief of his orthopnea. The medium moist râles, heard at the time of admission, receded but never completely disappeared.

On the second hospital day, several petechiae were noted on the dorsal surface of the right foot. A tourniquet test, bleeding, and clotting times were normal. Blood cultures were sterile. He appeared to be improving rapidly on the second and third days. Each day a few more petechiae appeared until at death on the seventh day, they were widely distributed over the body. None ever appeared on the mucous membranes or in the retinae. The blood pressure remained at 105/90, and the systolic murmur at the apex remained unchanged. The pulse was always regular.

On the fifth hospital day, the orthopnea and dyspnea again became uncomfortable. The patient experienced mild epigastric burning intermittently. The following day ankle edema became moderately severe, and at night he was disoriented. The presystolic gallop rhythm returned on the seventh hospital day. He began to yawn and became incontinent of urine. The ankle edema became severe, and medium moist râles could be heard over all parts of both lungs. He sank into coma and died on the seventh hospital day. Examination of the heart just before death revealed no abnormalities not present at admission. Neurological examination remained normal throughout.

Pathologic Findings.—At autopsy, petechiae were noted over the arms, trunk, and legs. There was pitting edema of the feet and ankles. The pleural cavities contained no fluid. The right lung weighed 700 grams, and the left lung weighed 600 grams. Both lungs were wet and congested on their cut surfaces.

The pericardial sac contained 500 c.c. of dark red blood and clots. The heart weighed 500 grams. There was an extensive infarction of the posterior surface of the heart that involved one-third of the posterior part of the right ventricle, the interventricular septum, and one-third of the posterior inferior part of the left ventricle. Through the lower posterior surface of the left ventricle, there was a ragged, irregularly-shaped rupture of the ventricular wall (Fig. 1). It measured 4 cm. by 1.5 centimeters. There was a second rupture measuring 3 cm. by 1.5 cm. at the base of the interventricular septum, making a passage between the left and right ventricles (Fig. 2). There was complete occlusion of the posterior branch of the right coronary artery, approximately 8 cm. from its orifice. The left coronary artery was patent, but there were many atheromatous plaques present. There were hemorrhages along the distribution of the posterior branch of the right coronary artery, as well as around the infarcted area. The wall of the left ventricle was 2 cm. in thickness, while that of the right ventricle was 0.5 cm. in thickness. There was one mural thrombus adherent to the wall of the right auricle and another adherent in the region of the infarction at the base of the right ventricle. There was calcification of the leaflets of the aortic valve, which prevented complete closure of the valve. Atheromatous plaques were noted in the free border of the mitral valve, as well as in the aorta.

The liver weighed 2,000 grams. The kidneys were grossly normal.

Microscopic examination of the sections of the heart showed an old thrombus with recanalization in the lumen of the posterior descending branch of the right coronary artery. A more recent thrombus superimposed on the old one was demonstrated in sections taken closer to the coronary orifice. There was extensive hemorrhage, muscle necrosis, and polymorphonuclear leucocyte infiltration in the walls of the right and left ventricles and the interventricular septum in the area of the infarction. A thrombus consisting of platelets, fibrin, polymorphonuclear leucocytes, and red blood cells was adherent to the endocardium of the right auricle.

In one section of the lungs, a small infarct of the pleura was seen and, in another section, an embolus consisting of fibrin, red blood corpuscles, and polymorphonuclear leucocytes was present in one of the small pulmonary vessels.



Fig. 1.—The posterior surface of the left ventricle showing the irregular longitudinal rupture (A).



Fig. 2.—The interventricular septum as seen from the right side of the heart, and showing a probe through the ovoid rupture of the interventricular septum.

The liver sinusoids were distended with red blood corpuscles in areas adjacent to the central veins, with necrosis of the liver cells bordering the central veins where the distention of the sinusoids was more marked. There was fat infiltration throughout the sections of the liver.

The walls of the arteries of the kidney showed thickening, and an occasional arteriolar lumen was obliterated.

Sections through the petechiae showed emboli consisting chiefly of fibrin located in the capillaries of the corium. There were hemorrhages adjacent to the capillaries.

DISCUSSION

Rupture of the anterior or posterior wall of the left ventricle is far more common than rupture of the interventricular septum. In 1925, Krumbhaar and Crowell¹ summarized all the cases of ventricular wall rupture from any cause and added twenty-two new cases. They were able to find 632 cases in the literature of the preceding fifty years. They tabulated the sex, age, duration of life following rupture, and the apparent exciting cause. They were unable to offer any explanation as to why some infarcted hearts ruptured and others did not.

In 1942, Edmonson and Hoxie² reported seventy-two cases of heart rupture of all types, of which thirteen were interventricular septal ruptures. They were able to make the diagnosis in three of their cases ante mortem. They emphasized the importance of keeping patients quiet after a coronary occlusion, especially for the first sixteen days, during which time ruptures were most likely to occur. They also pointed out that ruptures occurred three times as frequently in patients who had a hypertension of more than 140/90 following occlusion than in those who had normal blood pressure.

In 1943, Weber³ reported a case of interventricular septal rupture. He reviewed the literature up to that time and was able to find thirty-four cases. (Edmonson and Hoxie's cases were not included.) Few of these patients survived longer than a month. None suffered a second rupture. Only five were diagnosed before death. He was, however, able to diagnose his own case ante mortem. He pointed out that the diagnosis of interventricular rupture can be made when a loud systolic murmur and thrill develop suddenly after a known coronary thrombosis. A ruptured chorda tendineae or a ruptured papillary muscle, however, may give the same signs following a coronary occlusion.

In 1945, Segall⁴ discussed cardiac rupture and presented four cases. None of these were interventricular ruptures. He mentioned the difficulty in making the diagnosis ante mortem, but noted that sudden death preceded by sudden cardiac pain with severe dyspnea and shock occurring within the first two weeks of the onset of a coronary occlusion, is very suggestive evidence for a rupture of the ventricle with cardiac tamponade.

Levine⁵ warns against the use of stimulants in coronary thrombosis: "It is mainly with regard to the dislodgment of an embolus from the ventricular thrombus and rupture of the ventricle that stimulation is to be avoided." Both of these complications occurred in our case following the use of digitalis. For several days the digitalis produced improvement in the pulmonary congestion, as well as in the ankle edema. Whether the digitalis was ultimately harmful is a question which cannot be answered.

The petechiae were an unusual manifestation of embolism from mural thrombi. At autopsy they were found to have originated in the right auricle and ventricle, producing paradoxical embolism.⁶

SUMMARY

A case of coronary occlusion followed by rupture of the interventricular septum and later by rupture of the posterior wall of the left ventricle is presented. Paradoxical embolism was associated.

REFERENCES

1. Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, *Am. J. M. Sc.* 170:828, 1925.
2. Edmonson, Hugh A., and Hoxie, Harold J.: Hypertension and Cardiac Rupture, *AM. HEART J.* 24:719, 1942.
3. Weber, Manual L.: Perforation of the Interventricular Septum Following Infarction: Intravital Diagnosis, *Ann. Int. Med.* 19:973, 1943.
4. Segall, Harold N.: Rupture of the Ventricular Myocardium, *AM. HEART J.* 30:39, 1945.
5. Levine, Samuel A.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* 8:245, 1929.
6. Hirschboeck, Frank J.: Paradoxical Embolism, *Am. J. M. Sc.* 189:236, 1935.

ELECTROCARDIOGRAPHIC STUDIES OF GUNSHOT AND STAB WOUNDS OF THE HEART

HARVEY N. MIDDLETON, M.D.*
INDIANAPOLIS, IND.

TRAUMATIC injuries to the heart present a rare opportunity to observe clinically what has been accomplished experimentally in animals. The close observation of all such cases may do much to knit more closely the results of clinical cardiovascular examinations with the known pathologic physiology of the heart.

For more than forty years stab and gunshot wounds of the heart have been treated surgically. Davenport,¹ in 1924, reported the appearance of the typical electrocardiographic curves following ligation of a branch of the descending coronary artery and vein, after which similar reports were published by Elkins and Phillips,² Porter and Bigger,³ Koucky and Miles,⁴ and Davenport and associates.⁵

That an inflammatory reaction of the pericardium is a universal complication of penetrating injuries of the heart has been recognized for many years. Hesse,⁶ on the basis of a review of the aftereffects in twelve cases of his own and 107 cases from the literature, stated that the appearance of a dry pericarditis after heart suture could almost be considered a rule. Beck⁷ mentioned the high incidence of postoperative pericardial effusion and subsequent pericardial adhesions. In dogs, Barnes and Mann⁸ have shown that the mere opening of the pericardium resulted in extensive pericarditis.

The electrocardiographic changes produced by pericarditis consisted of early and transient elevation of the R-T segment in the first two, or in all three, leads.⁹ This elevation is generally most marked in Lead II, and aptly, therefore, has been called the T₂ type by Wood.¹⁰ The deviation is in the same direction (upward) in all (three) leads, unlike myocardial infarction where it is opposite in direction in Leads I and III. Also no significant Q pattern develops.

The electrocardiographic picture of acute myocardial injury, on the other hand, depends upon the location of the injury. Thus, an injury of the anterior left ventricular walls produces the characteristic T₁ type, with early upward elevation of the RS-T segment in Lead I. Infarction of the posterior or basal part of the left ventricle produces changes in the RS-T segment and T wave which are practically the reverse of those occurring in anterior infarction; the

Received for publication Dec. 14, 1946.

*From the Department of Medicine, Indianapolis City Hospital.

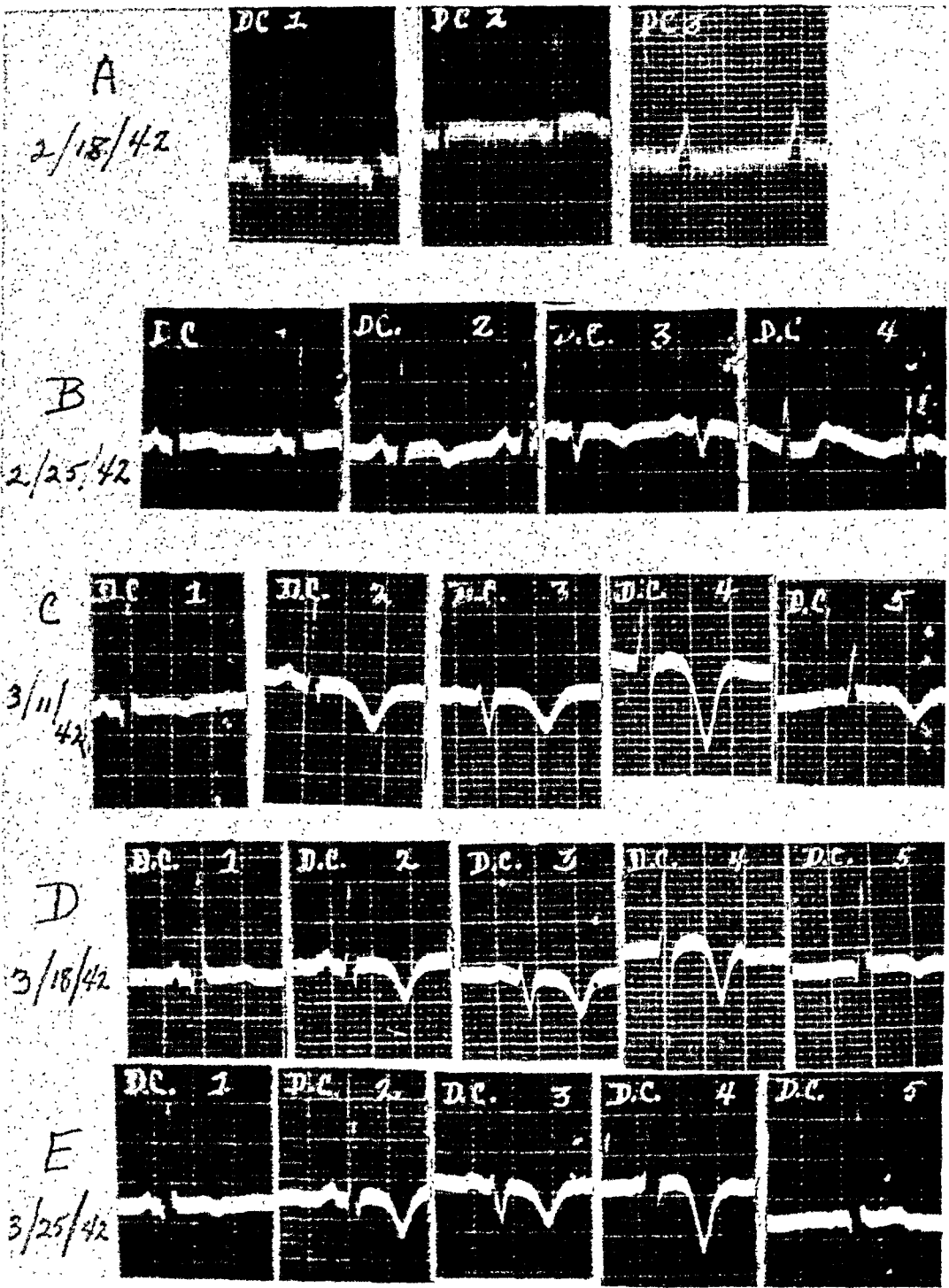


Fig. 1.—Case 1. D. C., a 26-year-old Negro man. Bullet wound, anterior axillary line. A, obtained three days after accident; B, obtained one week later; C, obtained three weeks later; D, obtained four weeks later; E, obtained five weeks later; F, obtained six weeks later; G, obtained three months later; H, obtained nine months later; I, obtained fourteen months later; J, obtained thirty-seven months later.

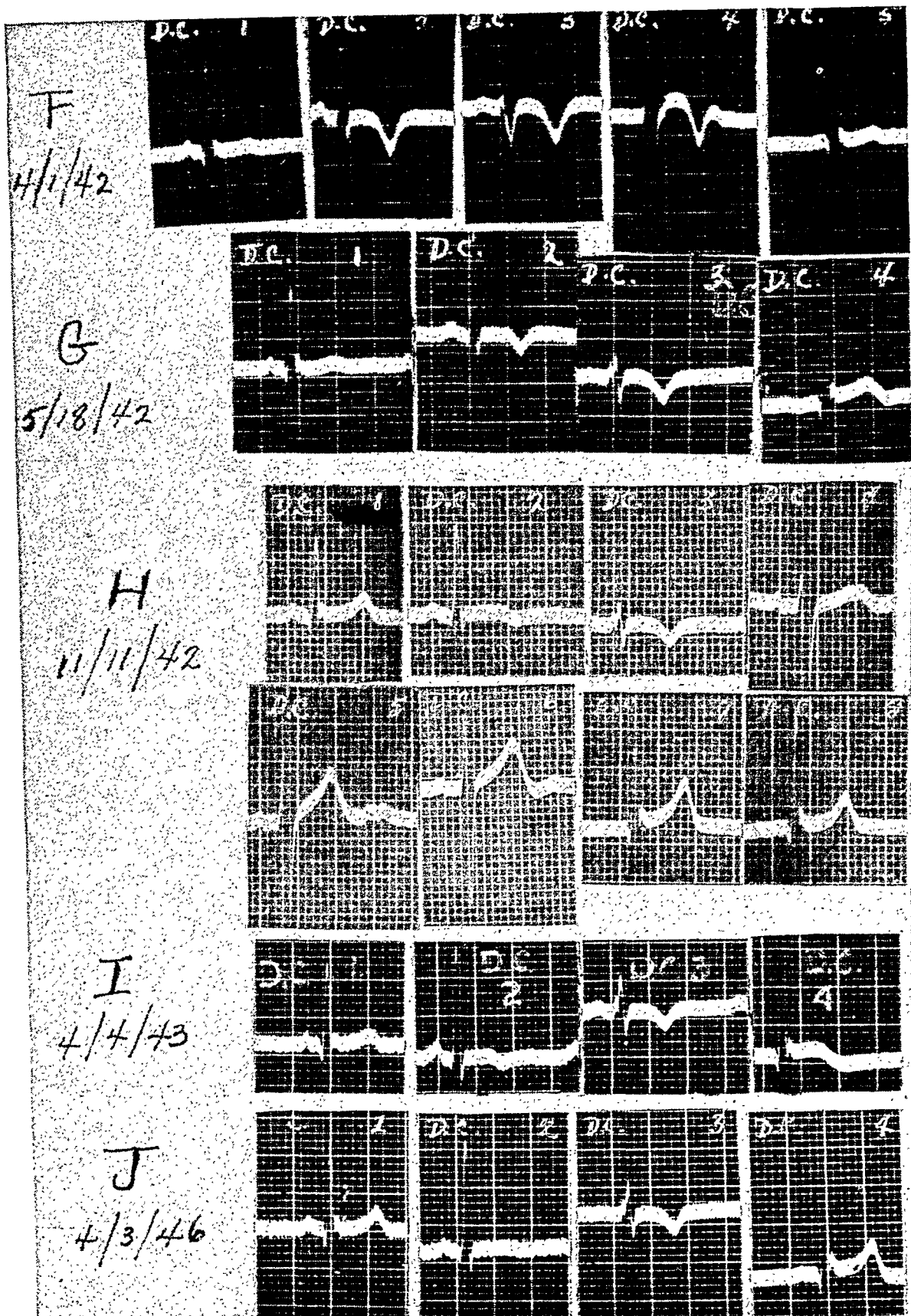


Fig. 1.—Cont'd. For legend see opposite page.

T₂ type (and usually the T₂ type) being inverted, and the T₁ type remaining upright. The RS-T shift is upward in Lead III and downward in Lead I.

Two case reports are presented from the records of the Indianapolis City Hospital. In the first patient, a pistol bullet pierced the anterior portion of the apex of the left ventricle and lodged in the pericardial sac; in the second patient the right auricle was injured by an ice pick.

CASE REPORTS

CASE 1.—D. C., a 26-year-old Negro man, was admitted to the Indianapolis City Hospital on Feb. 14, 1942, at about 11:00 P.M., after receiving a bullet wound in the anterior axillary line at about the fifth intercostal space.

On admission, he was in profound shock. His pulse rate was about 110 beats per minute and the heart sounds were distant. Fluoroscopy of the chest revealed a globular pericardial shadow with only slight movement.

A surgical operation* was started about an hour after admission. Upon entering the pericardium a large amount of fluid was encountered. At the tip of the left ventricle, three wounds were discovered, each approximately 1.0 to 2.0 cm. in length. Two of these were on the posterior surface of the apical region of the left ventricle, and one on the anterior surface. The posterior wounds were bleeding profusely. All of the wounds, and the pericardium as well, were closed with interrupted silk sutures. After operation, the blood pressure, which had been considerably lower, rose to 125/85.

Roentgenograms of the chest obtained two days, then one, two, and three weeks after the operation, revealed the cardiac shadow displaced to the right and pleural effusion of the left side.

Twelve electrocardiograms were obtained between the third day and thirty-seven months after the operation. Ten of them are shown in Fig. 1. In *A*, obtained three days after the accident, the RS-T segment was slightly elevated in Leads I and II and isoelectric in Lead III with a negative T wave. There was an S wave in Lead III. In *B*, obtained one week later, the RS-T segment was elevated in Lead I and depressed in Lead IV F. The T wave was inverted in Leads II and III. In *C*, obtained three weeks later, there was a cove-plane T wave in the limb leads and in Leads CF₂ and CF₄. In *D*, obtained four weeks later, there was a positive T wave in Lead I. In *E*, obtained five weeks later, there was a negative T₁ and a positive T₄. In *F*, obtained six weeks later, T₁ was positive and the T wave was less negative in Lead CF₂. In *G*, obtained three months later, there was an elevated RS-T segment in Lead IV. In *H*, obtained nine months later, there were less negative T waves in Leads II and III and taller T waves in Leads I and IV F. In *I*, obtained fourteen months later, there was a less positive T₁ and T₄. In *J*, obtained thirty-seven months after the operation, there were taller T waves in Leads I and IV F and diphasic T waves in Lead II.

CASE 2.—J. C., a 40-year-old Negro man, was admitted to the Indianapolis City Hospital on Aug. 14, 1943, about one-half hour after receiving a stab wound of the chest. On admission, he was in profound shock. The arterial blood pressure could not be recorded and the pulse was imperceptible at the wrist. The heart sounds were not audible. Fluoroscopy of the chest showed a quiet, dilated, globular heart. Forty minutes after admission, a surgical operation† was started. The pericardium was opened and a large quantity of blood freed. It was found that a cut approximately one-quarter of an inch in length penetrated the right auricle. Three sutures were used to close the wound. In ten minutes, the arterial blood pressure was 120/70. In two weeks, the patient was up in a wheel chair, and about ten days later, the patient was released after an uneventful recovery.

Roentgenograms of the chest were obtained one and two months after the operation and revealed clear lung fields, a transverse cardiac diameter of sixteen centimeters, and a "bottle-

*Performed by Dr. Wayne Carson, Indianapolis.

†Performed by J. R. Eastman, Jr., M.D., Resident in Surgery, Indianapolis City Hospital.

shaped" cardiac shadow. At the end of the second month, the transverse cardiac diameter measured fifteen centimeters.

Several electrocardiograms were taken over a period of two months after the operation, four of which are shown in Fig. 2. *A*, obtained three days after the operation, revealed that the RS-T segment was elevated 2.0 mm. above the isoelectric line in Leads I, II, and IV F, and isoelectric in Lead III with an inverted T wave and an S wave. The pulse rate was 100 per minute. In *B*, obtained one week later, the T waves were taller in Leads I, II, and IV F, and absent in Lead III. In *C*, obtained two weeks later, the T waves were inverted in Leads I, II, and IV F. The pulse rate was 100 per minute. In *D*, obtained eight weeks later, the T waves were positive in Leads I and II, diphasic in Lead III, and less negative in Lead IV F. In Lead III, the S wave was less than 2.0 millimeters. The P-R interval measured 0.24 second. The arterial blood pressure was 160/90. The pulse rate was 80 per minute. The transient changes in the electrocardiogram indicated acute pericarditis.

DISCUSSION

In the two patients there was no history of heart disease previous to the accidents, nor of any other illness which might have predisposed to such disease.

In Case 1, the electrocardiograms made from the third day to the thirty-seventh month after the heart wound showed progressive changes in the R-T segments and cove-plane T waves. In three months the T waves were positive in Leads I and IV F, and in the last electrocardiogram, the T waves were positive in Leads I, II, CF₂, and IV F, and negative in Lead III.

The unusual finding in these tracings was the fact that the cove-plane T waves were present in all leads. The electrocardiographic picture of acute myocardial injury of the anterior left ventricular walls usually produces the characteristic T₁ type, with the early upward deviation of the RS-T segment in Leads I and II and a downward displacement of this segment in Lead III, followed by the inversion of T₁ and T₂, with T₃ remaining upright. White¹¹ states that when T waves are inverted in all three classical leads, we are dealing either with multiple areas of infarction, coronary insufficiency, extensive pericarditis complicating infarction or occurring without myocardial infarction, or rarely, with myxedema. Thus, the three areas of infarction in this case were indicated by the cove-plane T waves in the three classical leads, and also in Leads CF₂ and CF₄. The prolonged duration of the changes of the RS-T segment suggest myocardial damage.

In Case 2, the electrocardiograms which were made from the third day until eight weeks after the injury showed changes in the RS-T segments and inverted T waves. On the third day, the RS-T segments were elevated 2.0 mm. above the isoelectric level in Leads I, II, and IV F; and for the next two weeks the T waves were inverted in the same leads and in Lead III, but less negative in Lead IV F. The P-R interval measured 0.24 second. The transient changes in the electrocardiogram suggested acute pericarditis.

Injury to the auricle alone is rare. On review of the literature, I found four cases with electrocardiographic tracings. The first case, reported by Glasser and associates,¹² was a gunshot wound of the left auricle in which they describe the changes of the electrocardiogram as resembling the changes of an anterior infarction. The second case, reported by Caviness and Turner,¹³ was a stab wound of the left auricle. They describe the changes in the electrocardiogram

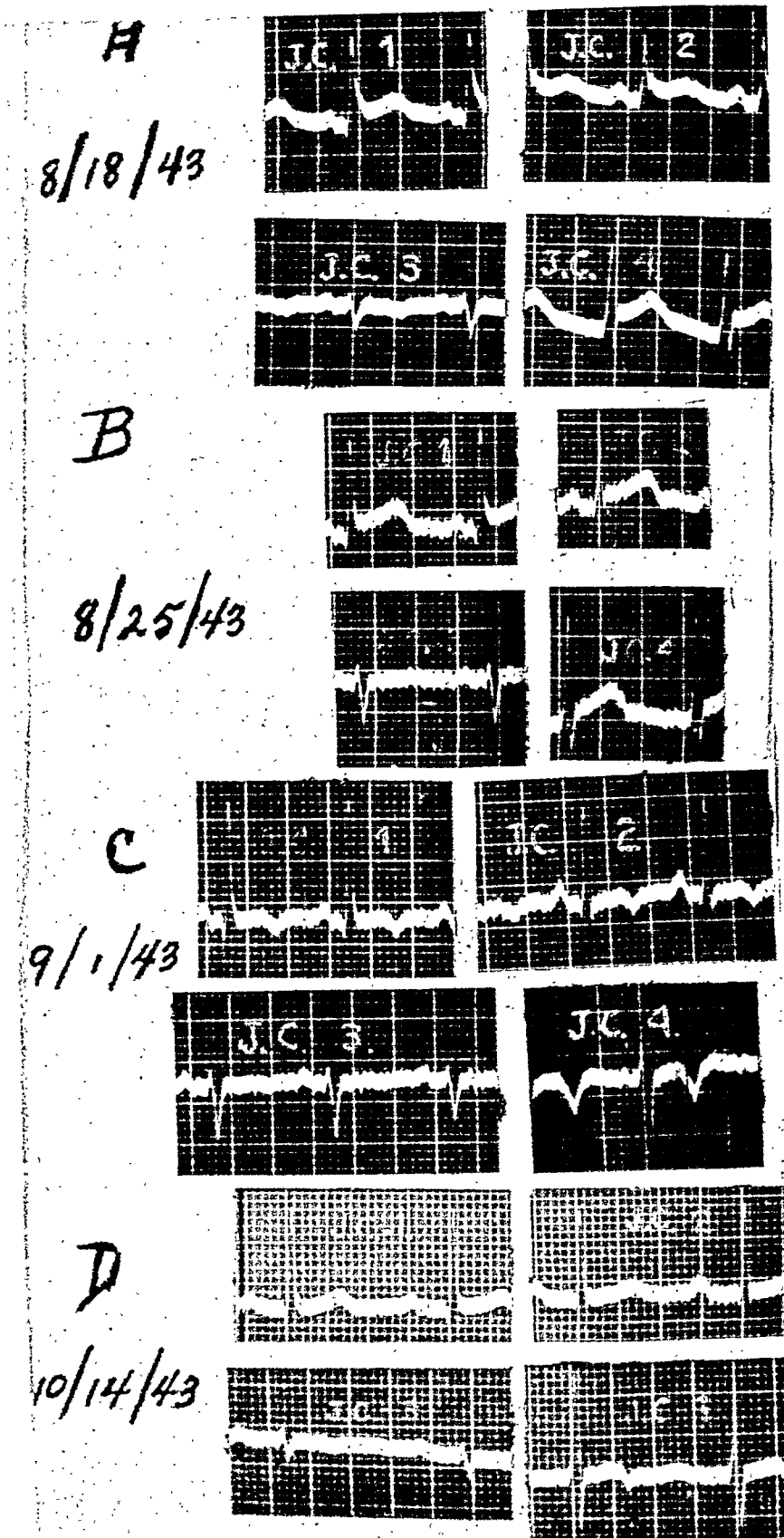


Fig. 2.—Case 2. J. C., a 40-year-old Negro man. Stab wound of the chest. A, Obtained three days after operation; B, obtained one week later; C, obtained two weeks later; D, obtained eight weeks later.

as those produced by coronary occlusion. There were inverted T waves in all leads. The third case, reported by Thompson,¹⁴ was a stab wound of the left auricle. There was inversion of the T waves in all four leads. He describes the changes as those of acute pericarditis. The fourth case, reported by Vander Veer and Norris,¹⁵ was a stab wound of the right auricle. An electrocardiogram made fifteen hours after operation revealed elevated RS-T segments in Leads I and II and some slurring of the descending limb of the R wave. They state that the changes in the electrocardiogram were due to acute pericarditis, and not to the injury of the auricle alone.

SUMMARY

The electrocardiographic studies of two patients with cardiac trauma, one with a gunshot wound of the apex of the left ventricle, and the other with a stab wound of the right auricle, are reported.

In Case 1, the electrocardiographic picture of acute anterior coronary infarction is in keeping with the preoperative diagnosis of three wounds, one on the anterior surface and two on the posterior surface of the apex of the left ventricle.

In Case 2, with a stab wound of the right auricle, the electrocardiographic changes reveal prolongation of P-R intervals to 0.24 second. The other changes in the electrocardiographic pattern may be attributed to acute pericarditis.

The author wishes to express his appreciation to Dr. Samuel A. Levine, Peter Bent Brigham Hospital, Boston, Mass., Dr. Irvine H. Page, Director of Research, Cleveland Clinic, Cleveland, Ohio, and Dr. G. W. Kohlstaedt, Medical Director, Eli Lilly Research Department, Indianapolis, Ind. for their many helpful suggestions.

REFERENCES

1. Davenport, G. L.: Stab Wound of the Heart, *J. A. M. A.* 82:1840, 1924.
2. Elkins, D. C., and Phillips, H. S.: Stab Wounds of the Heart; Electrocardiographic Studies of Two Cases, *J. Thoracic Surg.* 1:113, 1931.
3. Porter, W. B., and Bigger, I. A.: Non-Fatal Stab Wound of Ventricles, *Am. J. M. Sc.* 184:799, 1932.
4. Koucky, J. D., and Miles, G.: Stab Wounds of the Heart, *Arch. Int. Med.* 56:281, 1935.
5. Davenport, G. L., Blaumenthal, B., and Cantril, S.: Electrocardiographic Studies of a Stab Wound of the Heart, *J. Thoracic Surg.* 5:208, 1935.
6. Hesse, E.: The Functional Results of Wounded and Sutured Hearts in the Light of After Results of Heart Suture, *Deutsche Ztschr. f. Chir.* 193:239, 1925.
7. Beck, C. S.: Wounds of the Heart, *Arch. Surg.* 13:205, 1926.
8. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7:477, 1932.
9. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis, *J. A. M. A.* 113:1483, 1939.
10. Wood, P.: Electrocardiographic Changes of a T-2 Pattern in Pericardial Lesions and in Stab Wounds of the Heart, *Lancet* 233:796, 1939.
11. White, Paul D.: *Heart Disease*, Ed. 3, New York, 1944, The Macmillan Company, p. 496.
12. Glasser, S. T., Mersheimer, W. L., and Shiner, I.: Bullet Wound of Left Cardiac Auricle With Suture and Recovery; Review of Literature, *Am. J. Surg.* 53:131, 1941.
13. Caviness, V. S., and Turner, H. G.: Puncture Wound of Left Auricle, *AM. HEART J.* 25:693, 1943.
14. Thompson, L. L., Jr.: Stab Wound of Heart: Report of Successful Repair of Laceration of Left Auricle, *Pennsylvania M. J.* 48:218, 1944.
15. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis, *AM. HEART J.* 14:31, 1937.

THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN IN BEESWAX-PEANUT OIL: GLUTEAL ABSCESES AND RUPTURE OF THE SPLEEN

B. J. KENNEDY, M.D.,* AND JOHN SEED, M.D.†
BOSTON, MASS.

THE work of Romansky and Rittman¹⁻³ suggests that the intramuscular injection of penicillin in a beeswax-peanut oil mixture would be a convenient and effective method of administration in almost any condition in which the drug is indicated. However, a review of the literature reveals that there are several disadvantages in using this procedure in patients with subacute bacterial endocarditis. The case reported here presents an added objection.

The first point against the use of penicillin in beeswax-oil is that the large doses given by this method are less effective in producing an adequate penicillin blood level than is the prolonged intermittent administration of the same amount of penicillin in an aqueous medium. This has been pointed out by Kirby and associates.⁴ Apparently, when in contact with body fluids at body temperature, the penicillin in beeswax-oil is partially destroyed so that only one-half to one-third of the penicillin, as measured by present methods, reaches the blood.

A second point against penicillin in beeswax-oil is that the blood levels obtained with it are unpredictable. Kirby and associates⁴ found that 12 per cent of their patients had a blood level of less than 0.07 unit per c.c. four hours after the injection of 300,000 units of calcium penicillin in one c.c. of beeswax-peanut oil. Four hours was the time at which the average penicillin blood level was the highest, that is, 0.44 unit per cubic centimeter. Thirty per cent of their patients had no penicillin in their blood after twelve hours. Romansky and Rittman,³ using a slightly different method of measurement, obtained values just twice those of Kirby and associates. The peak blood level was at four hours, but the average value was 0.99 unit per cubic centimeter. Fourteen per cent had a level of 0.16 unit per c.c., or less, at four hours, and 30 per cent had no detectable penicillin in their blood after twenty-four hours. In contrast to the foregoing, continuous intravenous drip produces a blood level of about 0.1 unit for every 100,000 units administered in twenty-four hours, and the variations from this level depend primarily on controlling the rate of flow.^{5,6} A similar relationship holds for continuous intramuscular drip.⁷ The current trend in the treatment of subacute bacterial endocarditis is to give between 200,000 and 500,000, or

Received for publication Dec. 28, 1946.

*Assistant resident physician at the Massachusetts General Hospital, Boston.

†Formerly from the Massachusetts General Hospital, now serving in the United States Army Medical Corp.

more, units per day for three to eight weeks and to maintain at all times a blood level which is four to five times that of the sensitivity of the organism.⁸⁻¹¹ With penicillin in beeswax-oil, such a program requires frequent blood levels to determine the effectiveness of the therapy, and the beeswax-oil must be administered two to three times a day.

A third point against the use of this oil is that beeswax and peanut oil are foreign substances which can cause considerable tissue reaction. Romansky and Rittman² reported that after injection of a mixture of the two substances into the muscles of the hamster there was an infiltration of polymorphonuclear leucocytes about the injection site at the end of twenty-four hours with no evidence of muscle necrosis. By the tenth day after injection there were foreign body giant cells, mononuclear leucocytes, and oil cysts 1.0 to 2.0 mm. in diameter. By the twentieth day, there were minute cysts with fibrous walls, giant cells, and leucocytes. On the thirtieth day the cysts were partially collapsed and the giant cells still persisted.

A corollary of this third point is that these foreign substances are capable in some individuals of causing muscle necrosis and they may be conducive to abscess formation. Especially is this true in the treatment of subacute bacterial endocarditis where large amounts of the agent must be injected repeatedly for a long period. Denton¹² observed marked fibrosis of muscle in a patient suffering from subacute bacterial endocarditis. Denton's patient was given 300,000 units of penicillin in 1.0 c.c. of beeswax-oil twice a day for two months. The sites of injection were varied as widely as possible; but, nevertheless, at the end of this time the muscles became quite indurated, and contained firm nodules about 2.0 cm. in diameter. In spite of this he still had full use of his muscles. In view of the experiences to be quoted here it was believed that some of the nodules might have been the result of abscesses occurring at the sites of the penicillin in beeswax-oil injections; particularly since Denton's patient was not cured until penicillin was given by a different method.

REPORT OF A CASE*

A 17-year-old high school girl was admitted to the Massachusetts General Hospital because of low-grade fever, weakness, pallor, and swelling of the ankles.

At the age of 3 years, following acute appendicitis and appendectomy, she developed migratory polyarthrititis, a heart murmur, and chorea. This was diagnosed as rheumatic fever and she was kept in bed for six months. After that she was placed on slightly restricted activity and remained well until the age of 7 years. She then had a second episode of migratory polyarthrititis of unknown duration. Following this she was well until six months prior to admission, when she developed pain in the right leg radiating from the knee downward. This followed twisting her leg while swimming. The pain was relieved by manipulation by a chiropractor. Two weeks later she caught a "head cold" with fever of 99° to 100° F., and noted pain in the left upper abdominal quadrant on deep inspiration which lasted two days. Five months before admission she was admitted to another hospital because of a temperature of 101° Fahrenheit. She was given sulfadiazine for seven days during which time she developed a generalized skin eruption. The sulfadiazine was stopped and penicillin was given for three days. The fever disappeared and she

*This case was previously reported at the Massachusetts General Hospital Pathological Conference.²⁴

went home where she remained well until four months before admission, when she was again hospitalized for ten days because of a low grade fever and coryza. She was again treated with sulfadiazine and penicillin and remained well for two months. Two months before admission she began to have mild fever, muscle aches, cough, and minimal ankle swelling. She spent three weeks in bed, but when again ambulatory she continued to have ankle swelling that was relieved by rest. During the two weeks before admission her daily temperature varied from 98.6° to 101° Fahrenheit. The night before admission she was nauseated, vomited, and complained of abdominal pain. She had lost about 30 pounds during the six months' illness.

On physical examination she was found to be a pale, well-developed girl in no distress. The temperature was 99.6° F.; the pulse, 95 per minute; and the blood pressure, 130/80. On the cushion and tip of the left thumb there were two red, nontender, punctate areas. She had three carious teeth. The left border of the heart was 12 cm. to the left of the midline in the fifth intercostal space. There was a systolic apical thrill. A forceful mitral first sound was followed by a blowing Grade 4 systolic murmur. No diastolic murmur was heard. The pulmonic second sound was louder than the aortic second sound. The lungs were clear. The nontender tip of the spleen was felt. There was an appendectomy scar. No ankle edema was present.

On admission the erythrocyte count was 3.5 million; hemoglobin, 8.2 Gm.; leucocyte count, 21,700, with 82 per cent polymorphonuclear cells, 10 per cent lymphocytes, 7 per cent monocytes, and 1 per cent eosinophils. The urine was acid and the specific gravity, 1.020. One-plus albumin was found, and two red cells and twenty-five white cells were present in the sediment. The sedimentation rate was 1.45 mm. per minute (normal less than 0.35 mm. per minute). An electrocardiogram was normal with a rate of 100 per minute and normal P-R interval. A chest x-ray revealed a large left auricle posteriorly and elevation of the left main bronchus, consistent with mitral valvular disease.

On the second hospital day the petechiae on her thumb had disappeared and a red "spot" was found on the flexor surface of the right wrist. She vomited several times this day, but had no new complaints. The fifth day she felt well, though her temperature was 104.5° Fahrenheit. She had a slight nonproductive cough. There was definite dullness with bronchial breathing, increased whispered voice, and decreased tactile fremitus over the left lower lobe. A chest x-ray the following day verified the diagnosis of left pleural effusion with displacement of the heart to the left, suggesting the possibility of collapse of all or a portion of the left lower lobe. On the tenth day a shower of small petechiae appeared on the forearms and hands bilaterally and one small petechia in the right lower conjunctival sac. By the eleventh day ten blood cultures had been taken. Of these, two were sterile, one was negative for *Brucella* organisms, and seven were positive for alpha hemolytic streptococcus of the Lancefield Group A. By this time she was having daily temperature spikes of 103° to 104° F. rectally. Her pulse rate varied from 100 to 110 per minute. On the eleventh hospital day specific treatment was begun. This consisted of 300,000 units of penicillin in 1.0 c.c. of beeswax-peanut oil every eight hours intramuscularly. Fluids were limited to 1,800 c.c. daily. By the fifteenth hospital day, four days after the onset of therapy, her temperature was normal. She did very well until the twenty-fourth day when she had a slight temperature rise to 100.0° F. rectally. She complained of nausea, anorexia, and a periumbilical discomfort for one day only. For the next few days she also complained of a dull ache in the muscles of the right anterior thigh. At the time this was thought to be due to the penicillin injections. A throat culture grew out a few beta hemolytic streptococci. The penicillin sensitivity of the blood organisms was determined. The organism grew in 0.03 unit of penicillin and was inhibited by 0.06 unit. On the twenty-fourth hospital day the penicillin level in the blood at the end of eight hours (just prior to the next injection) was at least 0.06 unit per c.c. and less than 0.24 unit per cubic centimeter. A blood culture that day grew *Staphylococcus albus* (probably a contaminant). On the thirty-second day the penicillin level was less than 0.06 unit per c.c. at the end of eight hours. Benzoic acid, 2.0 Gm. administered three times a day by mouth, was then started.

On the thirty-sixth hospital day the patient complained of an aching pain in the mid-epigastrium and left epigastrium. There was no cough and the pain was questionably aggravated by respirations. The abdomen was soft but there was mild tenderness in the left upper quadrant. Peristalsis was slightly hyperactive. The dullness over the left lower lobe was unchanged from

the previous findings. She had no râles. The temperature was normal and the pulse rate varied from 90 to 100 per minute. This aching pain persisted slightly the next day. The leucocyte count was 20,000, with 73 per cent neutrophils, 13 per cent lymphocytes, and 14 per cent monocytes. In the evening of the thirty-seventh hospital day the patient suddenly clutched her left upper abdomen, vomited, and began writhing and groaning. She was pale, cold, and sweating. The heart sounds were rapid and regular. The chest remained unchanged. The abdomen was quite silent and only occasional tinkles were heard. There was no shifting dullness, spasm, or tenderness. She moved her arms and legs freely and all reflexes were equal. She opened her eyes in response to questioning. Oxygen was given and her color improved. She died twenty minutes after the onset of this episode.

Pathologic Report.—On opening the peritoneal cavity there were 600 c.c. of fresh blood and about an equal amount of clotted blood. The clotted blood obscured the spleen and extended down the left side of the abdomen into the pelvis. About the spleen were numerous dense, fibrous adhesions between the stomach, diaphragm, and parietal peritoneum. The surface of the spleen was ragged due to the adhesions, and just anterior to the hilum there was a deep red slit 2.5 cm. in length, which appeared to be the point of rupture into the peritoneal cavity. In the upper pole there was an abscess cavity measuring 4 x 2 cm. that contained yellow, purulent exudate. Cultures of this abscess revealed alpha hemolytic streptococci. In the lower pole there was a similar cavity measuring 6 x 3 cm. that was partially filled in with scar tissue and contained a small amount of purulent material in the center. In the center of the spleen there was an area 8 x 10 cm. in diameter composed of clotted blood. The splenic artery and vein were normal. There was no normal-appearing splenic tissue. The spleen weighed 630 grams. Microscopically, the cords of the spleen showed a fibrous thickening and many polymorphonuclear cells were present. Surrounding the areas of infarction there was increased fibrous tissue formation and an inflammatory cell reaction with polymorphonuclear cells and frequent phagocytes. There were numerous red cells.

On cut section of the kidney there was good delineation in all the kidney architecture, but the parenchyma appeared paler than usual. There were all degrees of glomerular hyalinization. Parts of the glomerular tufts were hyalinized, and in some glomerular spaces there was hemorrhage. The picture was consistent with healing embolic nephritis without fresh lesions. The right pleural cavity was normal.

The left pleural cavity contained dense fibrous adhesions between the parietal and visceral pleura over the left lower lobe, and between the left lobe and the diaphragm. The cavity contained 200 c.c. of clear, straw-colored fluid. Cut sections of the lungs revealed the parenchyma to be mottled pinkish-red and there were several small areas of atelectasis in the left lower lobe.

There was a small amount of fibrous adhesion between the visceral and parietal pericardium at the apex of the heart. The heart weighed 360 grams. The myocardium was paler than usual. The chordae tendineae of the aortic leaf of the mitral valve were somewhat shortened and thickened, and at the free edge of this valve there was a 2 x 3 mm. hard vegetation, the surface of which was rough and friable. The valve was also thickened. The remaining valves were normal. Microscopically, on the surface of the mitral valve there was a platelet thrombus incorporating bacterial masses with scarring and granulation tissue around them. Several giant cells were present. The thrombus was attached to the collagenous valve leaflet whose periphery was rather cellular. The process, therefore, appeared almost healed.

When an incision was made across each buttock to examine the injection sites of the penicillin in beeswax-oil, a large amount of purulent, yellow exudate oozed from the deep tissues. This exudate arose from numerous small abscesses in the substance of the gluteus maximus muscle and a few abscesses in the deeper layers of fat in the gluteal region. A culture of this revealed alpha hemolytic streptococcus, presumably the same organism that had been in the patient's blood stream originally. In several of these abscesses a darker-colored, thick oily fluid was also present, which had the appearance of the oil-beeswax vehicle that had apparently been injected directly into the previously formed abscesses. Microscopically, there was muscle necrosis and inflammatory reaction with foreign body giant cells, polymorphonuclears, lymphocytes, and histiocytes. There was also basophilic material present, presumably the wax in which the penicillin was incorporated.

DISCUSSION

Rupture of the spleen has been reported to be common in malaria, typhoid fever, pregnancy, parturition, acute infections, leukemia, typhus fever, infectious mononucleosis, relapsing fever, and many other conditions, but we have been able to find only ten reported cases in subacute bacterial endocarditis.¹⁶⁻²⁵

The histologic structure of the spleen facilitates bacterial embolism and infarction. Examination of the spleen in subacute bacterial endocarditis will reveal, in nearly all cases, the presence of small infarcts. The formation of a splenic abscess is the result of a septic embolus with necrosis and breakdown of the area of infarction.

Lake and co-workers,¹⁶ who reported the first case of ruptured spleen in subacute bacterial endocarditis, believed that the infected infarct had ulcerated through the splenic artery. This was also probably true in our case. Six of the ten cases reported in the literature had rupture of an infected infarct or frank abscess.^{16,17,20-23} The patient reported by Favour and associates⁹ had received intensive penicillin therapy, and at death the splenic infarcts and blood were sterile. Pallasse and associates¹⁹ gave as the cause of hemorrhage the rupture of a cortical infarct; Hertzog and co-workers,²⁵ the rupture of a hemorrhagic infarct. Krokeiwicz¹⁸ stated that the cause was due to paroxysmal increasing blood pressure when the patient strained during defecation. His patient was the only one of the ten to have proven involvement of the left pleura as a result of the subdiaphragmatic inflammation.

The reason for the choice of therapy in our patient was that the organism grew in 0.03 unit of penicillin per c.c. and was inhibited by 0.06 unit. Kirby and co-workers⁴ reported 96 per cent of their patients had a blood level between 0.04 and 1.0 units per c.c. eight hours after the injection of 300,000 units of calcium penicillin in beeswax-oil, and so it was believed that an injection every eight hours should prove sufficient. However, the precaution suggested by Keefer and associates¹³ of distributing the injection sites in the hips, arms, and thighs was not observed and injections were given alternately in each buttock. The bacterial endocarditis in our patient did respond to the penicillin therapy given. As was indicated in the pathologic examination, the lesions on the valve leaflets were almost healed.

The development of the alpha hemolytic streptococcus abscesses at the sites of penicillin injections has not been reported before. However, continuous intravenous or intramuscular drip has not infrequently been accompanied by considerable local reaction. Morgan, Christie, and Roxburgh,¹⁴ who first reported the use of continuous intramuscular drip, noted two abscesses due to *Coliform bacilli* around the site of the infection. Smith and Harford⁷ found that ten out of sixteen patients treated with continuous intramuscular drip developed severe local inflammatory reactions at the injection site at about the fifth to seventh day. This consisted of local leucocytosis, local pain, redness, heat, and swelling involving the whole lateral aspect of the thigh, all of which subsided in twenty-four hours after changing the injection site. Nelso-Jones and Williams¹⁵ reported a case of subacute bacterial endocarditis in which the

site of the continuous intramuscular drip was changed every four to five days, and twelve days after each site was changed a sterile abscess developed. This patient received 120,000 to 150,000 units of penicillin per day in the form of 1,000 units per c.c. in distilled water at pH 6.5. Fifteen c.c. of dark cream-colored, purulent fluid which was sterile aerobically and anaerobically was obtained from each abscess, which then proceeded to heal uneventfully.

The tissue reaction which occurred about the sites of injection of penicillin in beeswax-peanut oil was probably primarily due to the beeswax-peanut oil. The beeswax-peanut oil being a foreign body produced localized areas of necrosis which were easily invaded by bacteria producing abscesses. These abscesses were presumably infected by the organism of the blood stream despite the presence of penicillin in nearby tissues which apparently did not diffuse into the abscesses. Furthermore, much of the penicillin that was injected directly into abscesses already present was poorly utilized, if at all. Had aqueous penicillin been used perhaps these abscesses would not have occurred.

SUMMARY

1. Penicillin in beeswax-peanut oil led to the development of autogenous abscesses at the injection sites in a patient with subacute bacterial endocarditis. Death in this patient resulted from rupture of a splenic abscess.
2. Penicillin in beeswax-peanut oil is not the method of choice for the long-term treatment of subacute bacterial endocarditis.
3. A review of the literature on ruptured spleens in subacute bacterial endocarditis revealed only ten reported cases.

REFERENCES

1. Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin, *Science* 100:196, 1944.
2. Romansky, M. J., and Rittman, G. E.: Penicillin: 1. Prolonged Action in Beeswax-Peanut Oil Mixture, 2. Single Injection Treatment of Gonorrhea, *Bull. U. S. Army M. Dept.* 81:43, 1944.
3. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, *New England J. Med.* 233:577, 1945.
4. Kirby, W. M. M., Leiger, W., Martin, S. P., Rammelkamp, C. H., and Kinsman, J. M.: Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil, *J. A. M. A.* 129:940, 1945.
5. Rantz, L. A., and Kirby, W. M.: The Absorption and Excretion of Penicillin Following Continuous Intravenous and Subcutaneous Administration, *J. Clin. Investigation* 23:789, 1944.
6. Loewe, L., Rosenblatt, P., Russell, M., and Altire-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual Serum Levels of Penicillin: Comparative Studies With Particular Reference to Fractional and Continuous Intramuscular Administration, *J. Lab. & Clin. Med.* 30:730, 1945.
7. Smith, R. O., and Harford, C. G.: The Administration of Penicillin by Continuous Intramuscular Drip, *J. Lab. & Clin. Med.* 30:502, 1945.
8. Goerner, J. R., Geiger, A. J., and Blake, F. G.: Treatment of Subacute Bacterial Endocarditis With Penicillin: Report of Cases Treated Without Anticoagulant Agents, *Ann. Int. Med.* 23:491, 1945.
9. Favour, C. B., Janeway, C. A., Gibson, J. G., and Levine, S. A.: Progress in the Treatment of Subacute Bacterial Endocarditis, *New England J. Med.* 234:71, 1946.

10. Sigler, L. H., Thomas, J. L., and Feldman, H. H.: Treatment of Subacute Bacterial Endocarditis With Penicillin, *New York State J. Med.* 46:624, 1946.
11. Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* 129:1135, 1945.
12. Denton, J.: Private communication.
13. Keefer, C. S., Herrick, R. P., VanWinkle, W., and Putnam, L. E.: New Dosage Forms of Penicillin, *J. A. M. A.* 128:1161, 1945.
14. Morgan, H. V., Christie, R. V., and Roxburgh, I. A.: Experiences in the Systemic Administration of Penicillin, *Brit. M. J.* 1:515, 1944.
15. Nelso-Jones, A., and Williams, G. E. O.: Aseptic Necrosis at Sites of Continuous Intramuscular Penicillin Infusions, *Lancet* 2:817, 1945.
16. Lake, N. C., Kevin, H. K., and Irel, S.: Internal Hemorrhage From Splenic Infarct, *Lancet* 2:13, 1919.
17. Vallee, A.: Multiple Infarcts of the Spleen in Malignant Endocarditis; Rupture of the Spleen and Peritonitis, *Canad. M. A. J.* 9:1064, 1919.
18. Krokeiwicz, Anton: Spontaneous Rupture of the Spleen in Subacute Bacterial Endocarditis, *Virchows Arch. f. path. Anat.* 262:328, 1926.
19. Pallasse, E., Gueclaich, A., and Chapuis, A.: Spontaneous Hemorrhage and Capsular Rupture in Infectious Endocarditis, *Lyon méd.* 147:577, 1931.
20. Hicks, J. A. Braxton: Death From Rupture of an Infarcted Spleen in a Case of Malignant Endocarditis, *Brit. M. J.* 2:351, 1932.
21. Kerkhof, A., and Giere, E. K.: Rupture of Splenic Infarct in Subacute Bacterial Endocarditis, *AM. HEART J.* 8:423, 1933.
22. Fingerland, A.: Rupture of Spleen in Patient With Endocarditis Lenta, *Casop. lék. česk.* 77:422, 1938.
23. Rantz, L. A., and Kirby, W. M. M.: Enterococcic Infections. An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, *Arch. Int. Med.* 71:516, 1943.
24. Mallory, Tracy B.: Clinical-Pathological Conference, *New England J. Med.* 234:634, 1946.
25. Hertzog, A. J., Nesse, G., and Vandersleuis, Charles: Subacute Bacterial Endocarditis With Rupture of Spleen, *Minnesota Med.* 29:791, 1946.

Abstracts and Reviews

Selected Abstracts

Meccheri, L. A.: On the Pathological Variations of Venous Pressure. Publ. d. Centro de invest. fisiol. 9:237, 1945.

The author studied the value of venous pressure determinations in more than 100 cases with various cardiac and mediastinal syndromes. His conclusions are the following:

(1) A general increase of venous pressure is caused by cardiac disturbance, while a regional increase is due to compression of a collector. (2) General venous hypertension indicates heart failure; general venous hypotension, peripheral failure. (3) In diseases of the respiratory system, venous pressure determinations may be useful. Hypertension indicates cor pulmonale; hypotension, a peripheral disturbance. (4) Cardiac edema, cyanosis, and hepatic enlargement may be differentiated from other types by a high venous pressure, which is observed when these signs are caused by cardiac failure. (5) Serial determinations may help in the evaluation of cardiac failure and of the results of treatment. (6) Pleuropulmonary and mediastinal syndromes may cause regional changes of venous pressure. These may be evaluated only by measurements in different veins. (7) Increase of venous pressure in one venous collector may be the only sign of initial compression.

It should be noted that general venous hypertension, not connected with cardiac failure, may be found in tricuspid valve defects; in some cases of adhesive pericarditis; in some aneurysms (compression of the right auricle); in Lutembacher's syndrome; and, possibly, in auricular septal defects.

LUISADA.

Espersen, T., and Dahl-Iversen, E.: The Clinical Picture and Treatment of Pheochromocytomas of the Suprarenal. Acta chir. Scandinav. 94:271 1946.

The authors review the embryology, reported cases, and clinical picture of pheochromocytoma of the adrenal and add two cases of their own. The first, a man of 49 years with paroxysmal hypertension associated with violent headaches and cardiac irregularity, had a goiter and a basal metabolic rate of plus 30 per cent. The frequency of his attacks was reduced by thyroidectomy and he improved further on methyl-thiouracil, but eventual laparotomy revealed a 1,400 gram tumor. In the second case a boy of 10 years with permanent hypertension was explored through a left lumbar incision and no tumor could be found. Death a few hours after operation followed a shock state, and necropsy disclosed a small tumor in front of the great vessels and connected with the left adrenal by a small pedicle.

The level of epinephrine was found to be elevated in the blood of both patients, especially during attacks, and the tumors contained considerable amounts of it. The thyroid hyperplasia and improvement under antithyroid measures are attributed by the authors to a relation between the thyroid, adrenals, and hyperepinephrinemia analogous to that obtaining in certain cases of Graves' disease. They emphasize the value of methyl-thiouracil and preoperative attention to salt and water balance to minimize the danger of shock postoperatively. They now favor the abdominal approach for all cases.

SAYEN.

10. Sigler, L. H., Thomas, J. L., and Feldman, H. H.: Treatment of Subacute Bacterial Endocarditis With Penicillin, *New York State J. Med.* 46:624, 1946.
11. Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* 129:1135, 1945.
12. Denton, J.: Private communication.
13. Keefer, C. S., Herrick, R. P., VanWinkle, W., and Putnam, L. E.: New Dosage Forms of Penicillin, *J. A. M. A.* 128:1161, 1945.
14. Morgan, H. V., Christie, R. V., and Roxburgh, I. A.: Experiences in the Systemic Administration of Penicillin, *Brit. M. J.* 1:515, 1944.
15. Nelson-Jones, A., and Williams, G. E. O.: Aseptic Necrosis at Sites of Continuous Intramuscular Penicillin Infusions, *Lancet* 2:817, 1945.
16. Lake, N. C., Kevin, H. K., and Irel, S.: Internal Hemorrhage From Splenic Infarct, *Lancet* 2:13, 1919.
17. Vallee, A.: Multiple Infarcts of the Spleen in Malignant Endocarditis; Rupture of the Spleen and Peritonitis, *Canad. M. A. J.* 9:1064, 1919.
18. Krokeiwicz, Anton: Spontaneous Rupture of the Spleen in Subacute Bacterial Endocarditis, *Virchows Arch. f. path. Anat.* 262:328, 1926.
19. Pallasse, E., Gueclaich, A., and Chapuis, A.: Spontaneous Hemorrhage and Capsular Rupture in Infectious Endocarditis, *Lyon méd.* 147:577, 1931.
20. Hicks, J. A. Braxton: Death From Rupture of an Infarcted Spleen in a Case of Malignant Endocarditis, *Brit. M. J.* 2:351, 1932.
21. Kerkhof, A., and Giere, E. K.: Rupture of Splenic Infarct in Subacute Bacterial Endocarditis, *AM. HEART J.* 8:423, 1933.
22. Fingerland, A.: Rupture of Spleen in Patient With Endocarditis Lenta, *Casop. lék. česk.* 77:422, 1938.
23. Rantz, L. A., and Kirby, W. M. M.: Enterococcic Infections. An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, *Arch. Int. Med.* 71:516, 1943.
24. Mallory, Tracy B.: Clinical-Pathological Conference, *New England J. Med.* 234:634, 1946.
25. Hertzog, A. J., Nesse, G., and Vandersleuis, Charles: Subacute Bacterial Endocarditis With Rupture of Spleen, *Minnesota Med.* 29:791, 1946.

Abstracts and Reviews

Selected Abstracts

Meccheri, L. A.: On the Pathological Variations of Venous Pressure. Publ. d. Centro de invest. fisiol. 9:237, 1945.

The author studied the value of venous pressure determinations in more than 100 cases with various cardiac and mediastinal syndromes. His conclusions are the following:

(1) A general increase of venous pressure is caused by cardiac disturbance, while a regional increase is due to compression of a collector. (2) General venous hypertension indicates heart failure; general venous hypotension, peripheral failure. (3) In diseases of the respiratory system, venous pressure determinations may be useful. Hypertension indicates cor pulmonale; hypotension, a peripheral disturbance. (4) Cardiac edema, cyanosis, and hepatic enlargement may be differentiated from other types by a high venous pressure, which is observed when these signs are caused by cardiac failure. (5) Serial determinations may help in the evaluation of cardiac failure and of the results of treatment. (6) Pleuropulmonary and mediastinal syndromes may cause regional changes of venous pressure. These may be evaluated only by measurements in different veins. (7) Increase of venous pressure in one venous collector may be the only sign of initial compression.

It should be noted that general venous hypertension, not connected with cardiac failure, may be found in tricuspid valve defects; in some cases of adhesive pericarditis; in some aneurysms (compression of the right auricle); in Lutembacher's syndrome; and, possibly, in auricular septal defects.

LUISADA.

Espersen, T., and Dahl-Iversen, E.: The Clinical Picture and Treatment of Pheochromocytomas of the Suprarenal. Acta chir. Scandinav. 94:271 1946.

The authors review the embryology, reported cases, and clinical picture of pheochromocytoma of the adrenal and add two cases of their own. The first, a man of 49 years with paroxysmal hypertension associated with violent headaches and cardiac irregularity, had a goiter and a basal metabolic rate of plus 30 per cent. The frequency of his attacks was reduced by thyroidectomy and he improved further on methyl-thiouracil, but eventual laparotomy revealed a 1,400 gram tumor. In the second case a boy of 10 years with permanent hypertension was explored through a left lumbar incision and no tumor could be found. Death a few hours after operation followed a shock state, and necropsy disclosed a small tumor in front of the great vessels and connected with the left adrenal by a small pedicle.

The level of epinephrine was found to be elevated in the blood of both patients, especially during attacks, and the tumors contained considerable amounts of it. The thyroid hyperplasia and improvement under antithyroid measures are attributed by the authors to a relation between the thyroid, adrenals, and hyperepinephrinemia analogous to that obtaining in certain cases of Graves' disease. They emphasize the value of methyl-thiouracil and preoperative attention to salt and water balance to minimize the danger of shock postoperatively. They now favor the abdominal approach for all cases.

SAYEN.

Elmqvist, A., and Liljestrand, A.: On the Chemical Evaluation of Digitalis With the Baljet Reaction. *Acta physiol. Scandinav.* 12:53 (No. I), 1946

The Baljet reaction, a red-orange color formed when active cardiac glycosides are mixed with an alkaline picrate solution, has been modified in various ways since its discovery in 1918. The authors investigated the reliability of an electrophotometric technique devised by Bell and Krantz in 1939, which is claimed to possess accuracy comparable to that of cat biological assay. They report that the color was as strong in old solutions of *Digitalis purpurea* and *Digitalis lanata* as in fresh solutions, whereas the biologic potency, as assayed in guinea pigs, declined significantly. Warming the solutions further decreased biological assay activity, but the Baljet reaction was as intense as at room temperature. Digitonin (active) could be added to solutions without increasing the color reaction. It is concluded that the Baljet reaction is unreliable for clinical purposes.

SAYEN.

Trocmé, P. Micronodular and Reticulated Appearance of the Lungs During Acute Broncho Pulmonary Infection in a Patient With Mitral Disease. *Arch. d. mal. du coeur* 39:453 (Nov.-Dec.), 1946.

A case is reported in which the lung fields presented the peculiar granular appearance described a year ago by Leblanc as occurring in the course of mitral disease. In the present case, an x-ray film made during an attack of acute bronchitis in a patient who had mitral stenosis showed, in addition to reticulation, small shadows having the appearance of nodules scattered throughout the lung fields. As in Leblanc's case, the picture was strongly suggestive of tuberculosis, from which the condition may be difficult to differentiate. The peculiar lung shadows are evanescent.

LAPLACE.

Servelle, M. Lymphography and Elephantiasis. *Arch. d. mal. du coeur* 39:409 (Nov.-Dec.), 1946.

Lymphography is described as a new procedure of great value for physiopathologic study and for the diagnosis of elephantiasis, lymphedema, and related conditions. This report is concerned primarily with elephantiasis which is not an unusual condition in France.

Twelve cases of elephantiasis are reported, in eleven of which the lower extremity was involved. Extensive radiologic studies, including lymphography, were carried out. Commenting on these cases, the author states that he has found no evidence of deep venous thrombosis in any cases of elephantiasis, but that venography is essential to differentiate elephantiasis from postphlebitic edema which it resembles. There is risk of serious complications if the surgical treatment of elephantiasis is applied to postphlebitic edema.

Lymphography in cases of elephantiasis demonstrates dilatation and elongation of the lymphatics predominately on the internal aspect of the calf. The existence of marked lymphostasis is clearly demonstrated by making successive films during drainage of the contrast medium from the leg. It is uncertain whether the stasis is due to dilatation of the lymphatics or vice versa, but it is quite apparent that they coexist.

The pathogenesis of lymphedema is, in the majority of cases, an infection, sometimes due to insect bites involving the inguinal and retrocruial lymph nodes. The author does not believe any specific infection is involved. He emphasizes the necessity for special care in the treatment of inguinal adenitis in order to prevent elephantiasis. The relative effectiveness of the various operations designed to establish lymphatic drainage is discussed. Of these, two stage total superficial lymphangiectomy, although a relatively shocking procedure, has given excellent and, by far, the best results.

LAPLACE.

Lian, C., and Mantoux, G.: Syncope and Bundle Branch Block. *Arch. d. mal. du coeur* 39:438 (Nov.-Dec.), 1946.

Fourteen cases of syncope with associated bundle branch block are reported. These cases were of four types. (1) Persistent bundle branch block and complete A-V heart block. (2) Tran-

sient bundle branch block and complete A-V heart block, which were observed only during periods of syncope, the electrocardiogram being normal in the intervals between attacks. (3) Delayed A-V conduction with transient incomplete A-V block and bundle branch block. (4) Permanent bundle branch block with normal A-V conduction during the intervals between syncopal attacks. Of this last type, there were twelve cases; and in ten of these, the electrocardiogram was recorded during syncope and showed complete A-V heart block. In the majority of cases, death occurred within a few months or years after the onset of the syndrome. It is pointed out that in cases of normal rhythm with bundle branch block the occurrence of syncope is often attributable to a paroxysmal Stokes-Adams attack. Within a few months or years, the patient either dies or a permanent complete A-V heart block occurs.

LAPLACE.

Van Bogaert, A., and Van Genabeek, A.: Contribution to the Study of Electrocardiographic Abnormalities of the P-Q Interval. *Cardiologia* 11:255, 1946-47.

Two patients are presented who showed a second positive deflection (designated the X wave) after the P wave. The X wave closely resembled the P wave and followed it immediately. In the first case the X wave originated in Lead II from the isoelectric line immediately after P and had the same amplitude, but its descending limb was amputated in its middle by the ascending limb of R. After ten days of thyroid medication for postoperative myxedema it was evident that the X wave was actually the initial premature deflection of R, characteristic of the Wolff-Parkinson-White syndrome (W-P-W). In the second case, X was clearly visible in Leads I and II, but was of less constant amplitude. It originated below the isoelectric level, became positive, and finally continued on the isoelectric line with the ascending limb of R. Thus a Q wave was formed. This picture appeared shortly after an anterior wall infarct.

Without rejecting all the theories offered to explain the W-P-W syndrome, the authors suggest that the shortening of the P-Q interval and the lengthening of the QRS complex are only apparent and are the result of a supplementary X wave superimposed on the end of P-Q and the beginning of R. The X wave may be of auricular or ventricular origin.

The authors further point out that interference with the QRS-T complex by a slow auricular T wave can reproduce and explain all the known forms of the W-P-W syndrome. Depending on the amplitude, direction, and time relation of T_a with QRS-T, a simple Q wave, a descending staircase picture, or the minor forms of the W-P-W syndrome may appear. These anomalies of T_a are the expression of hyperexcitability of the auricular myocardium, which is manifested also by paroxysmal tachycardia and flutter or fibrillation. The cause may be anatomic or functional (coronary sclerosis, neurovegetative imbalance). The authors express their opinion that hearts with such manifestations cannot be considered normal in spite of the absence of other objective findings. Whatever causes the hyperexcitability may eventually cause a depression. Thus, diminished sinoauricular conduction, retarded sino nodal conduction, or shift of the pacemaker may result in shortening of the P-Q interval.

The previously mentioned anatomic and functional conditions may also cause hyperexcitability of the ventricular conduction system. A true shortening of P-Q results when the Tawara node is hyperexcitable. If one of the branches of the bundle of His is more excitable than the other, QRS occurs prematurely and P-Q is only apparently shortened. The proof of such origin is the persistence of the typical complex after suppression of auricular activity. In each case the changes after the initiation of the carotid sinus or oculocardiac reflex should be observed to determine the role of the auricle and the ventricle in the production of the syndrome.

The authors consider that the persistence in some cases of embryologic remnants of the auriculoventricular junction must be accepted with great reserve since no indication of their function exists in vivo.

LENEL.

Thordarson, O.: Clinical Studies on the Relative Incidence of Congenital Heart Disease. *Acta med. Scandinav.* 127:233 (No. III-IV), 1947.

The difficulties of estimating accurately the incidence of congenital heart disease are discussed and the relevant literature reviewed. The author found that of 31,771 hospital admissions

0.27 per cent had congenital heart lesions, or 1.8 per cent of those who had heart disease. Three-fourths of these patients had not been cyanosed or seriously hampered by their congenital heart lesions. The salient findings in eighty-four cases examined by the author are tabulated and the significance of various clinical symptoms discussed.

SAYEN.

Nylin, G., and Biörck, G.: Circulatory Corpuscle and Blood Volume in a Case of Patent Ductus Arteriosus Before and After Ligation. *Acta med. Scandinav.* 127:434 (No. V), 1947.

Study of the circulating blood volume by the radiophosphorus method for "tagging" red blood corpuscles (de Hevesy) confirmed previous observations by other workers, using the blue azo-dye technique, that there was a decrease after ligation of a patent ductus arteriosus. The red cell count decreased 8 per cent; the circulating blood volume, 12 per cent; and the roentgenographic heart volume, 19 per cent. The authors feel that their study supports the view that the blood volume is increased in shunts of the ductus arteriosus type.

SAYEN.

Espersen, T., and Jorgensen, J.: Electrocardiographic Changes in Paroxysmal Hypertension Due to Chromaffin Adrenal Tumor. *Acta med. Scandinav.* 127:494 (No. V), 1947.

The electrocardiographic findings in a case of paroxysmal hypertension due to pheochromocytoma of the adrenal and associated with thyroid hyperplasia are presented and discussed. Between attacks, tracings were normal or showed sinus tachycardia, auricular fibrillation, flutter, or sinoauricular block. Three tracings recorded during attacks of hypertension, headache, and palpitation showed auricular fibrillation with many deformed ventricular complexes in two instances, while on the third occasion atrioventricular dissociation was observed. Postoperatively, one tracing showed auricular fibrillation and subsequent recordings were normal. The Q-T segment and T-wave changes reported by other writers were not seen.

The authors concur with the view of others that the alterations in rhythm are produced by increased epinephrine content of the blood through "combined accelerans and vagus effect, the latter via the pressosensitive zones." They believe that the peculiarly characteristic electrocardiographic abnormality associated with pheochromocytoma is heterotopic stimulus formation, and that T-wave alternation, described by others, is probably associated with hypertension rather hyperepinephrinemia.

SAYEN.

Djin-Yuan Guo: Dissecting Aneurysm of the Aorta Related to Trauma. *Acta radiol.* 28:25 (No. I), 1947.

After citing instances of posttraumatic dissecting aneurysm from the medical literature, including three asymptomatic cases, the author reports the case of a 39-year-old farmer who fell off a horse in 1935, struck his chest on a stump, and fractured his sternum and some ribs. He recovered after "bilateral pneumonia." X-rays taken then (1935) showed a "double" aortic knob which was of similar appearance in 1944, save for calcification in part of the wall. In the oblique projection the calcified transverse and descending aorta could be seen to form a "camel's hump," a double angulation with a downward-bowed connecting link replacing the smooth curve of the aortic arch. The patient himself felt well and continued an athletic existence.

The rare but occasional occurrence of painless dissecting aneurysm of the aorta after trauma is emphasized as a possibility not often enough investigated by roentgenography in cases with clinical diagnoses of cardiac concussion.

SAYEN.

Lindgren, A.: Cutaneous Precordial Anesthesia in Angina Pectoris and Coronary Occlusion (an Experimental Study). *Cardiologia* 11:207, 1947.

Sixteen patients with the anginal syndrome were subjected to hypoxemia (breathing of a 10 per cent oxygen, 90 per cent nitrogen mixture) until angina occurred. The time of appearance

of pain was noted and the area of pain was mapped out on the skin. Electrocardiograms were taken at frequent intervals before, during, and after the test. The capillary oxygen saturation was also determined. The mapped out skin area was anesthetized by subcutaneous injection of 1 per cent novocaine without epinephrine. Most patients tolerated the hypoxemia longer after the anesthesia and the pain was less severe. In some patients the pain "migrated" outside the anesthetized area. In fourteen patients the electrocardiogram improved after anesthesia.

Eleven patients were made to exercise by bicycle until the appearance of pain. After anesthesia, with the same amount of work, seven patients remained free from pain and two were much improved. Nine showed significant improvement of the electrocardiogram. Two patients had relief of pain without change in the electrocardiogram. Two patients were anesthetized during spontaneous attacks of angina, after the recording of an electrocardiogram. Following the infiltration of the skin, the electrocardiographic changes and the pain disappeared.

The authors speculate whether their results signify improved coronary circulation, and whether cervicothoracic sympathectomy achieves the same results. Two patients subjected to the hypoxemia test before and after the operation experienced greatly reduced discomfort and milder electrocardiographic changes.

Five patients with acute myocardial infarction were anesthetized with LL30 (effective for five to six hours). The severe pain disappeared, leaving a sensation of dull substernal oppression. The pain reappeared but was less severe after the anesthesia wore off. The electrocardiographic changes were not affected.

LENEL.

Libbrecht, L., A Special Form of Essential Hypertension With Paradoxical Pharmacodynamic Reactions. *Acta clin. belg.* 2:106 (Jan.-Feb.), 1947.

A syndrome of essential hypertension is described in which the subcutaneous injection of 1.0 mg. of adrenalin is followed by paradoxical hypotension with bradycardia and paradoxical leucopenia with lymphopenia. Subcutaneous injection of atropine produces paradoxical stimulation of the gastric secretion. Reversal of the paradoxical reaction to adrenalin is produced by a preventive injection of atropine.

The probable mechanism and etiology of the paradoxical reactions are discussed. The author believes that a state of hypoparasympathicotonia is the basis of the syndrome for which he proposes the name "neurotonic hypertension."

LAPLACE.

Gobat, P. Y.: Variations of the Amount of Cytochrome-C in the Myocardium and in the Striated Muscle in Human Pathology. *Helvet med. acta* 14:45 (Feb.), 1947.

The following is a report of a study of the cytochrome-C levels in skeletal and heart muscle under normal and various pathologic states.

The cytochrome-C level of muscle is subject to individual variations. The myocardium, however, always contains more respiratory pigments than skeletal muscle. This difference is accentuated with age, and can be recognized very distinctly by an increase of the relation between cardiac and muscular cytochrome or C/M. This increased from 2.93 mg. per cent, between the ages of 20-30 years, to 3.77 mg. per cent, between 80-90 years, with its minimum between 50-60 years. This increase of the C/M results especially from a pronounced diminution of muscular cytochrome in old persons. However, cardiac muscle has a more or less constant requirement of catalysts for its cellular respiration. Hypertension causes an increase of heart respiratory pigments in relation to the muscular hypertrophy.

Children have only a small amount of cytochrome. But later in life the muscle fiber is rapidly enriched in cytochrome-C and contains the greatest amount between 20 to 30 years. Beyond this age, a tendency of progressive decrease can be observed in spite of the fact that a slight increase can be seen in persons from 50 to 60 years of age.

Diseases involving the whole body have a similar influence upon both cardiac and muscular cytochrome and the relation C/M presents an increase according to age both in sick and in healthy persons. Acute infections and even acute febrile infectious diseases possess hardly any influence

on the cytochrome level; whereas chronic diseases exert a very marked effect, especially infections with febrile courses, for example, tuberculosis which exerts an especially marked action.

In acute febrile infectious diseases this loss is certainly more pronounced, but cytochrome-C metabolism is a relatively slow process and the variations of the cytochrome level can be seen only after two to three weeks. Cancer also causes a diminution of the cytochrome level. In diabetes, the cytochrome level is sometimes reduced, whereas cases of uremia are accompanied by an augmentation of the respiratory pigments. Local alterations in the heart muscle can also modify the level of cellular respiratory catalysts and there is a distinct decrease of cardiac cytochrome in cases of myocarditis, fibrous and fatty degeneration of the myocardium, and coronary stenosis, whereas just the contrary can be seen in cases of arterial hypertension accompanied by hypertrophy of the heart muscle.

BELLET.

Chesley, L. C., and Annitto, J. E.: Pregnancy in the Patient With Hypertensive Disease. *Am. J. Obst. & Gynec.* 53:372 (March), 1947.

In a statistical analysis of 301 pregnancies in 218 patients whose histories established a diagnosis of "hypertensive toxemia" as defined by the American Committee on Maternal Welfare, the dangers of pregnancy in the hypertensive patient are clearly pictured. Only cases were included known to be hypertensive prior to pregnancy or in whom the diagnosis was made in the first twenty-four weeks. The standard for hypertension was taken as 140/90.

The frequency of Negro patients in the hypertensive group was more than twice that in total hospital admissions. In general, proteinuria varied directly with the degree of hypertension, though at least three-fourths of the patients were considered to have normal renal function. Pre-eclampsia was a complicating factor in 30 per cent of these cases. No clear-cut relation between the development of toxemia and the prepregnant or first trimester blood pressure could be made. Seventy-one per cent of hypertensive patients developing toxemia of pregnancy may be expected to have a recurrence in future pregnancies.

The hazards to the pregnant hypertensive are not great in two-thirds of the cases, but unfortunately the development of future pre-eclampsia or eclampsia cannot be predicted easily in a given case. The total maternal mortality in this group was twenty times that for the whole hospital experience, the fetal loss was ten times, and the incidence of toxemia was seven times that of the normal controls.

The mid trimester drop in blood pressure was of some diagnostic importance. If not recognized as such, the acute rise to be expected after the twenty-fourth week would lead in many cases to an erroneous diagnosis of pre-eclampsia. Further, a mid pregnancy rise in pressure was found to be ominous for future fetal prognosis.

KERN.

Sobin, S. S., and Landis, E. M.: Blood Pressure of the Rat During Acute and Chronic Choline Deficiency. *Am. J. Physiol.* 148:557 (March), 1947.

In view of the renal damage involving glomeruli which can be produced by diets deficient in choline, the authors attempted to study this deficiency in relation to hypertension. Male weanling rats were used. In acute choline deficiency, only six of eighteen rats survived, a mortality of 66 per cent. All the survivors had enlarged kidneys during the period of illness. However, there was no significant change in blood pressure.

Weanling male and female rats were used in the chronic experiments. At the end of five months, the systolic blood pressures of the choline deficient animals and the control group were the same. Therefore, in spite of the fact that the renal damage produced by choline deficiency persists for months and involves glomeruli as well as tubules, there is no hypertension produced. This suggests that the renal lesions resemble those of the nephroses.

BERNSTEIN.

Eckenhoff, J. E., Hafkenschiel, J. H., and Landmesser, C. M.: The Coronary Circulation in the Dog. *Am. J. Physiol.* 148:582 (March), 1947.

In these experiments the coronary blood flow was measured by the bubble flow-meter which was so inserted that one end was in the coronary artery to be studied and the other end in the carotid artery.

With this method, the so-called "normal" coronary flow was 65 c.c. per 100 grams of heart per minute. This figure varied little when the chest was either open or closed. Coronary flow is directly related to the mean arterial blood pressure with a fall in coronary blood flow with falls in blood pressure. Heart rate acceleration also increased coronary blood flow. Stimulation of the vagus or accelerator nerves had no significant coronary vasoconstrictor effect. Stimulation of the accelerator nerves did increase coronary flow, but usually only when blood pressure and heart rate also rose. In a few cases, however, there was acceleration of flow even without these changes. Stimulation of the vagus produced changes in coronary blood flow only when there were blood pressure or heart rate changes. Following atropine, stimulation of the vagus did not cause a reduction in coronary blood flow.

Ligation of one coronary artery caused no reflex vasoconstriction in five experiments. When the blood pressure began to fall, however, the flow began to decrease. Increasing the intrabiliary tension caused variable changes in the coronary flow, but they were always in the same direction as blood pressure change. Repeating the experiment after atropine, the changes of flow, blood pressure, and heart rate were not so marked.

In small doses, acetylcholine intraarterially increased the rate of flow. In larger doses, the increased flow was followed by a slowing. After atropine, acetylcholine was ineffective. Acetylcholine injected intravenously decreased coronary flow, probably due to the accompanying hypotension. Epinephrine increased coronary blood flow without significant change in heart rate or blood pressure, suggesting that this drug has a dilator effect upon the coronary arteries in small doses. In large doses its effect is probably due to increased cardiac metabolism.

It was found that the fraction of the cardiac output passing through the coronary arteries varies inversely with the cardiac output, so that under standard conditions the coronary arteries receive 4 to 5 per cent of the total cardiac output; but when the cardiac output fell to 500 c.c. or less per minute, more than 9 per cent of the total flowed through the heart. However, the actual flow per 100 grams of heart usually decreased as the output fell.

Coronary vessels are dilated by accumulated products of local metabolism. One hundred per cent oxygen decreased the rate of coronary blood flow. Carbon dioxide caused no consistent alteration in coronary flow when 5 to 7 per cent was used. Lowering of the blood pH caused no decrease in coronary flow, even though there was a drop in blood pressure.

BERNSTEIN.

Bruner, H. D., and Schmidt, Carl F.: Blood Flow in the Bronchial Artery of the Anesthetized Dog. *Am. J. Physiol.* 148:648 (March), 1947.

Bronchial artery flow was measured by the bubble flow-meter in fifty anesthetized dogs, in order to evaluate the role of bronchial artery flow in the etiology of paroxysmal and other types of pulmonary edema. Using P^{32} , blood flow was measured and it was found that 69 per cent of the blood flow through the right bronchial artery goes to the right lung and 31 per cent to the mediastinal structures. From this, they found that a factor of 1.26 times the observed right bronchial flow would approximate the total flow discharged into the pulmonary veins in a given dog per minute. Blood flow was highest during the beginning of the experiment and decreased with time. It appeared to be more closely related to cardiac output than to any other factors. The average flow was 0.3 per cent of cardiac output. The maximal flow was 2.0 to 2.5 times the average normal flow. They estimate that 30 to 40 c.c. per minute is the maximum total drainage into the pulmonary veins from both right and left bronchial arteries. This is about 1.25 per cent of the entire cardiac output and is considered to be insufficient to embarrass the drainage capacity of the pulmonary veins.

There was much spontaneous variation of bronchial blood flow. These changes were not related to blood pressure, spontaneous or pump ventilation, bilateral vagotomy, anesthesia, hem-

orrhage, or the amount of oxygen present, or movements of the larynx, esophagus, or other parts of the body. The source of the variations, therefore, appeared to be in the bronchial arteries themselves. The artery is dilated by fibers in the vagus and constricted by fibers in the accelerator nerve. However, two exceptions suggested the possibility that the accelerator nerve fibers are not exclusively constrictor. On the whole, however, the vagus is cholinergic and the accelerator essentially adrenergic. Response of this artery to drugs and abnormal oxygen and carbon dioxide tensions was much like that of other systemic arteries. From this data, it seems unlikely that increases in bronchial artery flow could overtax the drainage capacity of the pulmonary veins and raise pulmonary capillary pressure.

The distinctive feature of bronchial artery circulation seems to be its spontaneous variability. From a vasomotor innervation point of view it acts more like the splanchnic and peripheral arteries than the cerebral and coronary vessels. From the data, it would seem that bronchial flow to a given sector of lung would be so small as to inadequately maintain the alveolar structure in an area where pulmonary artery flow has been blocked or severely restricted. However, because the alveoli are independent of blood flow for their gaseous metabolic requirements, this small flow may be ample.

BERNSTEIN.

Opdyke, David F., and Foreman, Robert C.: A Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock. Am. J. Physiol. 148:726 (March), 1947.

The authors used an optical recording flow-meter of the perfusion type in which the rate of pressure decline within the meter is nearly proportional to the rate of inflow into the bed. This flow-meter is similar to that described by Green and Gregg, but differs in the method of operation. Control studies showed that coronary flow remained surprisingly consistent even with variations in blood pressure. Experiments showed that during the period of hypotension after hemorrhage the coronary flow is seriously curtailed. Immediately following reinfusion, and for some period thereafter, coronary blood flow is greater than during the control period, in spite of the fact that mean aortic pressure is slightly less than during the control period. Actual coronary flow is greater during shock than at similar levels of blood pressure in the preshock state.

This led the authors to conclude that there are no mechanisms operating which tend to reduce actual coronary flow other than loss of pressure head due to the decline of mean aortic pressure. Further, resistance to flow in the shock state is always less than control. Further, an inadequate coronary flow is not responsible for the circulatory failure following transfusion. It would appear, therefore, that myocardial damage in shock must come from a direct metabolic disturbance in the cells of the myocardium, resulting from the reduced coronary flow during the hemorrhagic hypotension period.

BERNSTEIN.

Eckstein, R. W., Wiggers, C. J., and Graham, G. R.: Phasic Changes in Inferior Cava Flow of Intravascular Origin. Am. J. Physiol. 148:740 (March), 1947.

The authors measured the pressure changes in the inferior vena cava by using a modified Pitot cannula. This cannula was provided with a small baffle plate on the afferent side and the tube on the efferent side was so placed as to transmit the pressure at the point of maximum blood velocity. This double tube was so adjusted that it did not interfere with natural flow as detected by rise of pressure in the abdominal inferior cava. Using this technique, it was found that the rhythmic fluctuations in flow in the inferior vena cava were proportional to the changes caused by systole and diastole in the auricle of the heart. Observation of the effect of diaphragmatic excursions showed that descent of the diaphragm increased the basic flow through the inferior vena cava significantly after a slight reduction at the beginning of descent. This effect occurred even after hemorrhage.

BERNSTEIN.

Casman, J.: Radiographic Demonstration of the Increase in Heart Volume After Ingestion of a Litre of Water. *Acta. clin. belg.* 2:113 (March-April), 1947.

Enlargement of the heart in persons who are heavy beer drinkers has been attributed to hydremia and to hypertension. An additional cause was suggested by Govaerts and Lequime, who found that drinking a liter of water was followed by an average of 20 per cent increase in the work of the heart. The possibility that the increased work is accompanied by enlargement of the heart was investigated by the author.

Twenty subjects, selected at random from a radiologic outpatient department, were studied. An x-ray film of the chest in the frontal plane was made before and forty minutes after drinking 1.0 liter of water. The duration of exposure included a complete cardiac cycle so that the cardiac silhouette could be measured in diastole. The measurements of three diameters were recorded: transverse, upper left to lower right border, and upper right to lower left border. After drinking the liter of water, these diameters were found to be increased by 5.31, 4.84, and 4.11 per cent, respectively. If the heart were spherical, an increase of 5 per cent in the diameters would indicate an increase of 15 per cent in the heart volume; when the increase in the diameters was maximum (10 per cent), the increase in heart volume would be 33 per cent.

It is concluded that when absorption of liquid is excessive, it may lead to the marked cardiac enlargement which characterizes the "beer heart."

LAPLACE.

Marshall, F. A.: Tetany Following Mercurial Diuresis. *J. A. M. A.* 133:1007 (April 5), 1947.

The author presents the case of a 60-year-old woman who had been treated over a period of five months for congestive failure by digitoxin and repeated mercurial intramuscular injections. The patient suffered recurrent episodes of congestive failure and nocturnal dyspnea, and had been vomiting in spells. During one of these attacks of failure, the calcium was 7.4 mg. and phosphorus, 5.5 mg. per 100 cubic centimeters. Mercurial diuretics (mersalyl and mercurphylline injections chiefly) had been given at intervals of three to ten days as required by edema and congestive failure.

On three separate occasions, tetany followed the parenteral use of mercurial diuretics. The author stresses the need for thought on the mobilization and excretion of electrolytes other than the chlorides. Relief was obtained through the use of parenteral and oral calcium. It appears that tetany is more likely in patients who ordinarily have a borderline calcium deficiency, which is further reduced below this critical level by excessive diuresis.

BELLET.

Krieger, V. I., and Weiden, S.: The Value of the Cold Pressor Test in the Prediction of Hypertension and Toxemia in Pregnancy. *Med. J. Australia* 1:417 (April 5), 1947.

The authors report that in a series of 522 cold pressor tests performed during 200 pregnancies, all tests gave normal results in eighty-four instances; hyper-reaction to the cold stimulus occurred in one test only on each of thirty-one patients, and in more than one test on each of eighty-five patients. Of all patients whose cold pressor tests gave normal results, only thirteen developed hypertension in the later stages of their pregnancies. In four of these patients the hypertension was associated with pre-eclampsia. In those patients in whom only one test gave a result of the hyper-reactive type, half had a normal pregnancy; the other half developed either hypertensive toxemia or pre-eclampsia. When mild hyper-reaction occurred on more than one occasion, twenty-six of the eighty-five patients had a normal pregnancy, but forty-nine developed hypertensive toxemia, and ten had pre-eclampsia. In the hands of the authors, the cold pressor test has given consistent results throughout pregnancy in the majority of their cases, and erratic results have been the exception.

The results of cold pressor tests performed two and twelve months after delivery are valuable in assessing the prognosis of subsequent pregnancies. Those patients who still show hyper-reaction twelve months after delivery should probably be classified as hypertensive. In the cases in which the hyper-reaction response is replaced by a normal response some time after delivery,

it can be assumed that the abnormal response during the pregnancy was caused by some specific agent which may not be active in a subsequent pregnancy.

The authors feel that the results of serial cold pressor tests during pregnancy are of value to the obstetrician, since, even if only one response in the series is of the hyper-reactive type, 50 per cent of the patients giving such responses develop hypertensive or pre-eclamptic toxemia. When two or more abnormal results are obtained, the number of patients who develop such toxemia increases to nearly 70 per cent. On the other hand, toxemia occurs later in the pregnancy in only a few patients in whom the response to the test is always normal.

Follow-up tests two and twelve months after delivery are sometimes helpful in assessing the prognosis of subsequent pregnancies, since patients who have hypertension, or are likely to develop it, can be differentiated from those unlikely to have this complication.

BELLET.

Bartholomew, R. A.: The Possible Etiologic Significance of Thrombosis of a Placental Vein on the Mechanism of Placental Infarction and Associated Toxemia of Pregnancy. *Am. J. Obst. & Gynec.* 53:650 (April), 1947.

In a case of acute fulminating toxemia developing at term in a 28-year-old nullipara, pathologic examination of the placenta showed thrombosis of a vein on the fetal surface with an associated broad area of plainly demarcated acute infarction. The author advances the belief that such thrombosis was causative of the subsequent acute toxemia, arguing that placental tissue has been shown to possess a high content of arginine together with arginase, an enzyme theoretically capable of producing guanidine, a known eclamptogen. Thus, hypothetically, autolysis of necrotic villi produced by such thrombosis could result in the dissemination of poisonous protein split-products into the maternal circulation with widespread damage to liver and kidneys which could provoke an ultimate eclamptic state.

KERN.

Wastl, H.: Observations of Influence of Corn-Silk Extract (*Stigmata Maydis Zeae*) on Blood Pressure in Hypertensive Rats. *Arch. Internat. de pharmacodyn. et de therap.* 74:1 (April), 1947.

The author studied the influence of injections of corn-silk extract (*Stigmata maydis zeae*) on the blood pressure of rats rendered hypertensive by looping a stout cotton thread over the poles of both kidneys (method of Grollman and Harrison). One c.c. per 100 Gm. of rat, or 0.1 mg./kg. of corn-silk extract in aqueous solution, 1.10⁵ concentration, was injected intraperitoneally and its effects studied. The hypertensive rats were divided into three subgroups; rats with slight hypertension (0 to 20 per cent), rats with medium hypertension (plus 20 per cent to plus 40 per cent), and rats with marked hypertension (over plus 40 per cent). The percentage figures represent the permanent increase over the respective individual normal blood pressures. Pretreatment observations were followed by four consecutive days of injections and then wound up by four consecutive days of posttreatment observations.

No significant influence on the blood pressures of normotensive rats was observed. Hypertensive animals, however, responded with a moderate reduction of blood pressure. The average declined by 15.0, 13.2, and 12.8 mm. Hg in the slight, medium, and marked hypertension groups, respectively. A return to the preinjection pressure level was complete on the second day after cessation of the injection. No adverse effect whatsoever was observed.

The most favorable results as regards decreases of the levels of systolic blood pressures, were achieved with the combination of hydrobromide paredrine and with S-Benzyl-iso-thiourea-hydrochloride. Somewhat less effective is a second pair, corn-silk extract and S-Methyl-iso-thiourea sulphate. The present report, dealing with corn-silk extract, shows that it has certain possibilities in the alleviation of human hypertension.

BELLET.

Kelly, H. G., Gibson, W. C., and Meakins, J. F.: Cerebral Air Embolism Following Artificial Pneumothorax Treatment With Prolonged Inhalation of Oxygen. *Canad. M. A. J.* 56:388 (April), 1947.

A 28-year-old woman who had been suffering from bilateral apical tuberculosis was given a routine pneumothorax refill. As the needle was withdrawn the patient went into a violent convulsion. These seizures recurred at short intervals for a period of three hours. On the following day she was still in deep coma but was breathing regularly and freely. The left extremities were unresponsive and lifeless. Treatment with a mixture of carbon dioxide and oxygen, and later 100 per cent oxygen, resulted in gradual improvement with return of consciousness. Residual apathy, drowsiness, and confusion gradually disappeared. Six days after the preceding episode, the patient was well.

Electroencephalograms obtained over a period of six months showed obliteration of normal cortical activity, which gradually returned toward normal.

BELLET.

Rees, H. C., and Slevin, J. G.: Surgical Management of Vascular Leg Ulcers. *Surgery* 21:575 (April), 1947.

The authors discuss the various procedures utilized in the treatment of ischemic and varicose ulcers. With regard to local therapy the first aim is to combat infection, a frequent complication. For this purpose, the authors have found a solution of gentian violet painted on the ulcer, combined with a light dusting with sulfathiazole crystals, to be quite effective. The systemic use of sulfonamide compounds has not been found to be as efficacious as their local application because the local blood supply is generally impaired. However, prolonged topical use of these substances will inhibit epithelization. Another procedure which has certain advantages over the local use of sulfonamides is a new soluble dressing containing a nitrofurantoin compound. After infection is controlled, the authors have found that pressure dressings, in the form of soft sponged rubber, applied to the ulcer site and held in place by a cotton elastic bandage helped to hasten the healing of the lesion. In those instances in which the etiological factor is a varix feeding the involved site, the affected veins should be ligated, with subsequent injection of any remaining varicosities with a sclerosing solution. This step should be delayed until infection is under control.

In those instances in which the ulcer persists after adequate treatment, other causes should be sought, such as arteriosclerosis obliterans or the presence of scar tissue surrounding the ulcer and interfering with the local blood supply. In case dense scar tissue is present, it may be necessary to resort to plastic operations on the ulcer, consisting of an elliptical incision around the ulcer including the margin of scar tissue. The incision is carried down to the deep fascia. The wound is allowed to form healthy granulations which are subsequently skin grafted. In most instances such an extensive plastic operation is not necessary, and healing can be brought about with skin grafting alone. This procedure not only lessens the period of disability by weeks but also affords the best insurance against recurrence. The most successful skin graft method, according to the authors, is the pinch graft type. When dealing with leg ulcers in patients with a history of an old deep phlebothrombosis, the results with the usual procedures are generally poor. The authors have found that in such instances ligation of the femoral vein below the profunda and also the saphenous veins improves the circulation and permits successful skin grafting of the ulcer site.

ABRAMSON.

Parker, R. L., and Barker, N. W.: The Use of Anticoagulants in the Management of Acute Myocardial Infarction: A Preliminary Report. *Proc. Staff Meet., Mayo Clin.* 22:185 (May 14), 1947.

The use of dicumarol and heparin in the management of acute coronary thrombosis with myocardial infarction is based on four principal objectives: (1) prevention of an extension of the thrombus; (2) prevention of the formation of intracardiac mural thrombi; (3) prevention of thrombophlebitis from which pulmonary embolism may arise; and (4) prevention of thrombosis

in peripheral arteries already considerably affected by arteriosclerosis. The purpose of this preliminary report is to present the authors' experience in the first fifty cases of acute myocardial infarction in which these preparations were used. The series of 100 cases reported by Nay and Barnes is used as a control series.

In ten cases, heparin was used in combination with dicumarol; in forty cases, dicumarol was used alone. When heparin is employed, an immediate anticoagulant effect is obtained. When dicumarol is used alone, there usually is a lapse of approximately thirty-six to forty-eight hours before the prothrombin level is reduced sufficiently to prevent intravascular clotting. Twenty patients in this series obtained an adequate anticoagulant effect within forty-eight hours after the onset of acute myocardial infarction. In eighteen cases a period of two to five days elapsed before an adequate effect was obtained and in twelve cases there was a lapse of more than five days. In no instance was a serious complication encountered as the result of anticoagulant therapy.

Two patients in this series of fifty cases had secondary vascular complications while they were receiving anticoagulant therapy during their convalescent period in the hospital, in comparison with 37 per cent of the patients who had such complications in the control series in which anticoagulants were not used. The difference in the mortality rate in respect to patients treated with anticoagulants and those not so treated was not notably different: 10 per cent and 13 per cent, respectively. It would seem, therefore, that although there was a marked reduction in the incidence of thromboembolic complications among the patients who received anticoagulant therapy, there was little influence on the total mortality rate.

BELLET.

Chesley, L. C., Annitto, J. E., and Jarvis, D. G.: A Study of the Inter-Action of Pregnancy and Hypertensive Disease. *Am. J. Obst. & Gynec.* 53:851 (May), 1947.

In a continuing study of 301 pregnancies in 218 patients with hypertension, an attempt was made to determine the effect of pregnancy on hypertensive disease. The study showed that the majority (66 per cent) of hypertensive women apparently were not jeopardized by pregnancy, though in the one-third that did not escape superimposed toxemia, the incidence of maternal and fetal mortality was greatly increased over that of the whole hospital experience. Of the total 218 cases accurately followed up to 1946, 17.9 per cent were dead; of the one-third who developed superimposed toxemia along with their hypertension, 31.7 per cent were dead; of the remaining two-thirds who did escape superimposed toxemia only 9.6 per cent were dead.

Statistical analysis and clinical study of this carefully followed group of patients led the authors to conclude that repeated pregnancies are not demonstrably harmful to the hypertensive woman, though pregnancy itself is hazardous should toxemia occur.

KERN.

Davis, M. E., and Wortmann, R. F.: Subacute Bacterial Endocarditis During Pregnancy. *Am. J. Obst. & Gynec.* 53:878 (May), 1947.

Following a protracted sore throat in the thirty-second week of her third pregnancy, a 31-year-old woman was admitted to a hospital for study. The heart was found to be 40 per cent oversize by x-ray. Other positive findings were a loud, harsh heart murmur replacing the first sound at the apex and an abnormal patency of the eustachian tubes. Three weeks later the heart size had increased to 60 per cent above normal and repeated blood cultures were positive for *Streptococcus viridans*. During a course of thirty-six days, 45,850,000 units of penicillin were administered together with repeated small blood transfusions. Following the subsidence of the acute infection, a cesarean hysterectomy was performed in the thirty-eighth week of pregnancy because of two previous sections for cephalopelvic disproportion and to decrease the hazard of postoperative infection. Recovery was uneventful, the patient being discharged on her forty-fifth postoperative day with repeated negative arterial and venous blood cultures, a normal white count, and a near-normal sedimentation rate. During the subsequent year there was no recurrence of the subacute endocarditis, though the heart remained enlarged and showed findings typical of mitral disease. The spectacular recovery did not forestall serious residual cardiac damage.

KERN.

Honigman, A. H., and Karns, J. R.: Healed Subacute Bacterial Endocarditis: Report of Two Cases With Death Due to Congestive Heart Failure. *Ann. Int. Med.* 26:704 (May), 1947.

Two patients having subacute bacterial endocarditis, in whom the diagnosis was confirmed by the recovery of *Streptococcus viridans* from the blood stream, ultimately succumbed to congestive heart failure even though all clinical and laboratory evidences of persisting infection were eradicated by adequate amounts of penicillin. Autopsy examination was made in one of the cases. This revealed thickening of the free margins and adherence of the commissural portions of the aortic valve cusps, thickening and nodularity of the mitral valve, and tiny grape-like clusters of densely scarred calcified material on one of the adjoining chordae tendineae. Histologic study of these calcified nodules showed their structure to consist of dense scar tissue, traversed by endothelial and thick walled vessels, and extensive deposits of calcareous material. In various sections made through these fibrocalcareous vegetations, organisms could not be demonstrated by hematoxylin and eosin stain or Glynn's stain for bacteria.

WENDKOS.

Weintraub, H. J., and Bishop, L. F.: The Anoxemia Test for Coronary Insufficiency. *Ann. Int. Med.* 26:741 (May), 1947.

The anoxemia test was employed for the study of patients with and without stigmata of coronary artery disease. The former group consisted of twenty adults who suffered from angina of effort and most of whose electrocardiograms were significantly abnormal, while the latter group, who were used as controls, included 200 patients who did not suffer from angina of effort even though fourteen of this number had various types of cardiovascular abnormality. The criteria of a "positive test" were those which had previously been established by Levy and co-workers.

As advocated by Levy, the test was not performed soon after the ingestion of food, in the presence of congestive heart failure, or within four months after known cardiac infarction. Repeat tests were never done on the same patient. If chest pain resulted during the test, it was discontinued and 100 per cent oxygen was immediately administered. In spite of these precautions, untoward effects were encountered not infrequently, both in the control group and in those exhibiting angina of effort. In a quantitative sense, there were 108 slight, thirty-seven moderate, and six severe reactions in the former group, and six slight, seven moderate, and two severe reactions in the latter group. In a qualitative sense, the reactions were quite variable. The most common symptoms were headache, dizziness, numbness, tingling, drowsiness, air hunger, and cyanosis. In the two instances in which twitchings of the extremities occurred, this symptom was abolished by the inhalation of 100 per cent oxygen. Chest pain also was relieved by similar means.

Of the twenty patients in whom a diagnosis of coronary artery disease seemed to be unequivocal prior to the performance of the test, eleven showed significant electrocardiographic changes following exposure to the low oxygen mixture. During the test, eight of these eleven cases, in addition, developed pain in the chest, six in less than ten minutes and two within ten to twenty minutes. In seven of the twenty patients with coronary disease, the electrocardiogram remained unchanged, but precordial pain appeared before twenty minutes of exposure. A negative electrocardiographic response and absence of pain were encountered in two of the twenty cases with coronary artery disease. Of the twenty patients with coronary artery disease, the control electrocardiogram was abnormal in thirteen instances. In eight of this latter group, electrocardiographic changes presumably indicative of transient myocardial ischemia developed. Analogous changes occurred in only three cases of the seven who had a normal control electrocardiogram.

In the 200 normal controls, the test did not provoke any chest pain. In this same group, electrocardiographic changes developed in nine. In seven of these nine cases, there were abnormal cardiovascular, hemic, or emotional factors present. In the other two of these nine cases no such factors were present.

Of the 191 normal controls who showed a negative electrocardiographic response, according to the criteria of Levy, there were twenty-three instances of T-wave changes primarily involving

the T waves in Leads I and IV and consisting of notching, a diphasic configuration, and flattening. No explanation for these minor T-wave changes is offered.

WENDKOS.

Stein, M. H., and Driscoll, R. E.: Paroxysmal Ventricular Tachycardia With Acute Left Ventricular Failure in a Patient With No Evidence of Organic Heart Disease. *Ann. Int. Med.* 26:769 (May), 1947.

Following a drinking bout, an 18-year-old soldier developed an attack of sudden cardiac acceleration, chest pain, and moderate dyspnea for which he was immediately hospitalized. Similar attacks, lasting from ten minutes to ten hours and unrelated to alcohol, had recurred at variable intervals ever since the age of 5 years. These episodes always ceased spontaneously and did not result in any further disability. At the time of his hospital admission, the physical examination revealed a heart rate of 200 per minute with a regular rhythm. One hour following his admission, he suddenly developed an even greater cardiac acceleration associated with orthopnea, cyanosis, and cough productive of large amounts of bloody, frothy sputum. The examination at this time revealed the typical findings of pulmonary edema. Emergency treatment was given and an electrocardiogram made shortly thereafter showed the presence of what was interpreted to be ventricular tachycardia with a rate of 230 per minute. Twelve hours after admission, the paroxysm of tachycardia subsided and an electrocardiogram made then showed the presence of a sinus rhythm with a rate of 110 per minute and no changes in any of the auricular or ventricular deflections. The physical examination at that time revealed no abnormal findings. Repeated clinical examinations and laboratory studies of the heart were normal and failed to indicate any form of organic heart disease.

WENDKOS.

Reitman, N.: The Antistreptolysin Titer as a Diagnostic Aid in Carditis of Obscure Etiology. *Ann. Int. Med.* 26:774 (May), 1947.

A 15-year-old schoolboy developed an acute febrile illness, during the course of which inconstant systolic basal and apical murmurs were audible. There were no joint pains, epistaxis, rash, or abdominal pain to suggest the diagnosis of acute rheumatic fever. An electrocardiogram at the beginning of the illness showed a bizarre disturbance of rhythm, which seemed to be the result of a wandering pacemaker, and frequent premature contractions. Because of these findings, a diagnosis of acute carditis of undetermined cause was made and prolonged bed rest was advised. Three days following the original record, another electrocardiogram was made which showed a normal sinus rhythm with a heart rate of 60 per minute and normal auriculoventricular conduction. Another tracing made two weeks later was essentially unchanged. Approximately one month following the onset of the illness, the cardiac murmurs had disappeared. Antistreptolysin titers during the period of observation rose significantly. Follow-up examination several years later revealed no signs of valvular heart disease. He served as a combat infantry soldier during World War II and suffered no disability during this military service. The author concluded that the rise in antistreptolysin titer, and conjunction with the disturbance of cardiac rhythm demonstrable in the electrocardiogram, and the temporary systolic murmurs establish the fact that the acute febrile illness, during which the above phenomena were encountered, was an episode of acute rheumatic fever. Furthermore on the basis of his experience with this case, the author suggests that antistreptolysin titer determinations may prove to be a useful diagnostic aid in other cases of acute carditis of obscure etiology.

WENDKOS.

Clark, J. H., Nelson, W., Lyons, C., Mayerson, H. S., and De Camp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient. *Ann. Surg.* 125:618 (May), 1947.

The authors describe a syndrome consisting of weight loss, decreased blood volume, decreased blood proteins (including hemoglobin and plasma proteins), and increased interstitial

fluid volume and call it "chronic shock." The importance of a reduced blood volume is seen in the tendency for the chronically ill patient to go into shock during major surgical procedures. Reduced blood volume is readily correctable by whole blood transfusions.

Many surgical conditions may result in a state of chronic shock. Among the most important are the following: malignancies, especially of the gastrointestinal tract, chronic sepsis, and hepatic disease.

The authors present considerable data to show that the hematocrit and plasma protein determinations fail to reveal the underlying deficit in blood volume and hence total blood hemoglobin and total plasma proteins. They also demonstrate that total hemoglobin suffers more than total plasma protein in the chronically ill patient. Blood volume is correlated more closely with the percentage of weight lost from the normal for any given individual than with other methods of estimation, such as surface area, age, sex, and height.

Therapeutically, whole blood transfusions of 500 ml. to 1,000 ml. daily are the best means of preparing a chronically ill patient for a major surgical procedure. Amounts of blood from 1,500 ml. to 4,000 ml. may be necessary.

LORD.

Freeman, N. E.: Direct Measurement of Blood Pressure Within Arterial Aneurysms and Arteriovenous Fistulas. Surgery 21:646 (May), 1947.

Freeman employed an aneroid manometer attached to a three-way stopcock, which in turn was connected to a 20-gauge needle and a 10 c.c. syringe. After the aneurysm or fistula had been exposed, the component vessels were controlled by means of rubber tubing. The end of the needle was then inserted into the aneurysm or fistula and the blood pressure noted. Additional readings were taken when the proximal artery and then the distal artery were occluded, and also when both vessels occluded. In cases with an arteriovenous fistula further studies were carried out with the vein occluded.

Twenty-three patients were studied. The mean initial pressure in the group with the arterial aneurysm averaged 84 mm. Hg with variation of 110 to 34 millimeters. When the afferent artery was occluded, the pressure fell to an average of 59 mm. of mercury. In the group of patients with arteriovenous fistulas, the mean initial pressure averaged 40 mm. Hg with variations between 70 and 30 millimeters. With constriction of the afferent artery the pressure fell to an average of 10 mm. of mercury. The author believes that the lowest safe mean arterial pressure after excision of an aneurysm or arteriovenous fistula is approximately 32 mm. of mercury.

Direct measurement of arterial pressures at the time of operative management is helpful in evaluating the adequacy of the collateral circulation.

LORD.

Shaffer, J. O.: A Method of Rapid Transfusion Into the Femoral Vessels In Patients Without Adequate Peripheral Superficial Veins. Surgery 21:659 (May), 1947.

A relatively simple technique is described for inserting and immobilizing a number 20-gauge needle in the common femoral vein or femoral artery. Each needle is inserted vertically just below the inguinal ligament until its lumen is in the desired vessel, and held by 3 hemostats placed at right angles to the tube 120 degrees apart. The clamps are taped to the skin.

The method has great value when a patient is in need of blood or plasma and all of the superficial veins are occluded. In cases of profound shock the femoral artery is employed.

LORD.

Shaffer, J. O.: Intra-Arterial Penicillin in the Surgical Treatment of Infections of the Extremities. Surgery 21:692 (May), 1947.

The author utilized intra-arterial injection of penicillin in local infections of the extremities, in order to obtain a higher concentration of the drug in the affected tissues than could be hoped to be reached by intravenous or intramuscular administration. With such a procedure, dilution of the penicillin is minimal, and at the same time the blood pressure forces the concentrated drug

into the local area supplied by the artery. The factor of increased capillary permeability, resulting from the inflammatory process, permits a greater filtration of the agent locally.

The technique of administration consisted first of producing vasodilatation of the vessels of the involved extremity, either by the subcutaneous injection of papaverine hydrochloride or by soaking the limb in a warm 1:9000 potassium permanganate solution for 20 minutes. A blood pressure cuff was placed around the extremity proximal to the infected portion and inflated to a pressure of 80 mm. Hg; and then the injection into the artery was made over a period of ten seconds, using a 20-gauge needle, 2 inches long. Routinely, a dosage of 50,000 units of penicillin in 10 c.c. of saline solution was given. The pressure in the cuff was maintained at 80 mm. Hg. for ten minutes after the termination of administration of the drug. Injections were given once or twice daily.

The author found that diabetic gangrene, and gangrene due to arteriosclerosis and frostbite with associated infection, osteomyelitis, suppurative joints, infected ulcerations of the legs and feet, and infected operative incisions all responded well to intra-arterial administration of penicillin. The procedure effectively overcame the difficulties offered by tissue barriers and vascular impairment which reduced the efficacy of penicillin administered intravenously or intramuscularly. As a result, various types of infection, with or without tissue necrosis, were effectively controlled, thus obviating surgery in many instances, simplifying it in some, and altering it from an emergency status to an elective procedure in others. Phlebothrombosis and infection at the site of injection were found to be contraindications to the use of intra-arterial administration of penicillin.

ABRAMSON.

Bauersfeld, S. R.: Dissecting Aneurysm of the Aorta: A Presentation of Fifteen Cases and a Review of the Recent Literature. Ann. Int. Med. 26:873 (June), 1947.

The data available in the cases of fifteen patients having dissecting aneurysm, in all of whom the diagnosis was confirmed by necropsy, are presented. Hypertension was definitely known to exist in eight cases. A diastolic aortic murmur was noted in four instances. In five cases chest roentgenograms were made, and varying degrees of aortic widening were noted in three of this number. Electrocardiograms were made in four cases; in two of this number, depressed S-T segments in Leads II and III were noted but no correlation between these changes and the autopsy findings is made. In addition, the author includes an excellent discussion of the clinical features of dissecting aneurysm.

WENDKOS.

Baker, L. A., and Musgrave, D.: A Study of Mitral Stenosis in Patients Who Survived the Age of Fifty. Ann. Int. Med. 26:901 (June), 1947.

The authors studied 106 patients with mitral stenosis, uncomplicated by other valvular lesions, who had lived beyond the age of 50 years. The diagnosis was based on the presence of a diastolic rumble at the apex. This was usually associated with an accentuated sharp first heart sound. Only thirty-two gave a definite history of antecedent rheumatic infection. Of this number, rheumatic fever occurred before the age of 20 years in eighteen, before the age of 10 years in seven, and in the remaining seven after the age of thirty. Only nine patients had any knowledge of a cardiac lesion before the age of thirty.

Fifty patients of the group reached the age of 50 years without subjective manifestations of heart disease. In four patients, more than eighteen years had elapsed between the initial discovery of a valvular lesion and the subsequent development of cardiac symptoms. In four cases, the first difficulty consisted of hemiplegia, vertigo, hemoptysis, and acute coronary thrombosis, respectively. The complication of subacute bacterial endocarditis occurred in only one instance. Chronic nontuberculous pulmonary disease, supposedly related to healed rheumatic pulmonary lesions, was frequently an associated finding and in twenty-nine of this number much of the respiratory distress could be blamed on pulmonary emphysema, chronic bronchitis, or pulmonary fibrosis. Chest roentgenograms were available in eighty-one of the patients, and in sixty-six instances there was definite x-ray evidence of pulmonary emphysema or abnormal bilateral

pulmonary fibrosis. The authors suggest that the cardiac failure may be due, in part, to the complicating pulmonary lesions which add another burden to an already strained right ventricle. Embolic phenomena, most often resulting in hemiplegia, occurred in eighteen patients, but auricular fibrillation was an associated finding in only ten cases of this number. Of the entire group of 106 cases, chronic auricular fibrillation existed in sixty patients. An abnormal cardiac silhouette was evident in most, but not all, of the eighty-one patients in whom roentgenograms of the chest had been made. In thirty-six instances the cardiac configuration was typical of mitral stenosis. In nineteen others, the enlargement was predominantly that of the left ventricle, presumably due to a high degree of mitral insufficiency. In the entire series, the blood pressure of only thirty-two patients was found to exceed 150 systolic or 90 diastolic, and in only eighteen did the diastolic pressure exceed 100 millimeters. Among the thirty-two patients with hypertension, marked cardiac enlargement was present in twenty. A similar degree of enlargement was noted in only twenty-one of the seventy-five patients with a normal blood pressure. The electrocardiograms did not prove to be an important diagnostic aid, since right axis deviation occurred in only one-third of the cases. The findings in precordial leads are not mentioned.

Of the forty-four patients who were known to be dead at the time this report was prepared, the average age at death was 52.8 years, the oldest patient being 64 years of age. The most common cause of death was congestive heart failure, which varied in its duration from six months to ten years in different cases. Embolic episodes accounted for six deaths; subacute bacterial endocarditis, pneumonia, and malignancy were responsible for the remainder. The cause for the relatively benign course of the disease in the group of patients who formed the subject of this report remains a matter for speculation. The authors suggest that a mild initial rheumatic infection, unsucceeded by subsequent rheumatic episodes, permits a slow progressive valvular deformity to develop without much myocardial injury so that heart failure is delayed until the dynamics of the circulation are sufficiently disturbed by the valvular lesion.

WENDKOS

Rogers, H. M.: The Cardiovascular Manifestations of Induced Thyrotoxicosis; Report of Two Cases. *Ann. Int. Med.* 26:914 (June), 1947.

Two cases are presented in whom auricular fibrillation developed after the ingestion of excessive amounts of desiccated thyroid substance. In both instances, discontinuance of the thyroid extract resulted in prompt resumption of normal sinus rhythm and disappearance of cardiac decompensation. The first case was that of a 63-year-old white woman who apparently had no organic heart disease and yet suffered from congestive failure induced by the thyrotoxicosis and auricular fibrillation. The second case was that of a 60-year-old white woman who also showed a bundle branch block in electrocardiograms made during the periods of auricular fibrillation and normal sinus rhythm, and yet did not develop congestive heart failure during the time she had auricular fibrillation.

WENDKOS.

Coller, F. A., Campbell, K. N., Berry, R. E. L., Sutler, M. R., Lyons, R. H., and Moe, G. K.: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease, and Other Painful States. *Ann. Surg.* 125:729 (June), 1947.

The authors investigated the therapeutic effects of tetra-ethyl-ammonium, a new compound, which has been found to block transmission of nerve impulses through autonomic ganglia. It was noted that parenteral injection of the drug in animals produced a fall in both systolic and diastolic blood pressure and an increase in peripheral blood flow, although it had no direct effect on arterioles. Furthermore, it did not prevent the direct peripheral action of epinephrine in raising blood pressure. In man, in addition, tetra-ethyl-ammonium produced dilatation of the pupil, loss of accommodation, cessation of sweating, dry mouth, and postural hypotension. No action of the drug could be demonstrated in a sympathectomized extremity.

Tetra-ethyl-ammonium was administered clinically, either intramuscularly or intravenously, in the form of a 10 per cent solution. The intravenous dose ranged from 100 mg. to a maximum of 500 milligrams. The authors utilized the drug in a series of patients suffering from causalgia

and related post-traumatic painful states and noted that in half of these, sustained relief of symptoms followed repeated injections. However, it was the opinion of the authors that autonomic blockades resulting from the use of the drug, which produced symptomatic relief in this group of patients, did not remove the indications for appropriate sympathectomy. Nevertheless, where the latter procedure was not feasible because of the presence of a marked psychogenic element or unstable personality, the use of tetra-ethyl-ammonium was indicated. In the case of herpes zoster and postherpetic neuralgia, some relief of pain, varying from a very brief period to six hours per block, was obtained in every instance, although more sustained improvement occurred in the patients with acute or subacute herpes zoster.

The authors found that in functional vascular disease, such as abnormal responsiveness to a cold environment, tetra-ethyl-ammonium was of diagnostic value, but it left much to be desired as a therapeutic measure. However, it was felt that in certain of the patients with Raynaud's phenomenon, attacks were aborted or modified in intensity.

In the case of organic occlusive arterial disease, tetra-ethyl-ammonium was utilized as a therapeutic agent in that it relieved vasospasm, caused some relief of pain, and improved claudication. It was also of help in determining which patients might derive benefit from sympathectomy. Those with early to moderately advanced thromboangiitis obliterans experienced definite improvement either in the degree of pain or in the severity of claudication. However, in the case of the far advanced process with or without established gangrene, or in the presence of severe infection, the drug was of no avail. In the case of arteriosclerosis obliterans, it aided in the control of nocturnal pain but generally was of little value in improving claudication.

Tetra-ethyl-ammonium was utilized in individuals suffering from acute and chronic deep thrombophlebitis. An excellent response was noted in the instances of acute and subacute cases in the form of relief of pain and reduction of edema. The patients suffering from the sequelae of deep thrombophlebitis noted subsidence of edema and relief from pain and vasospasm. For the most part, the therapeutic effect was only temporary.

The authors advocated caution in the use of the drug in hypertensive patients, particularly in those in whom a neurogenic component existed. Precipitous falls in blood pressure on occasion occurred in these individuals, with temporary peripheral circulatory collapse. Elderly patients generally did not respond as well as did those in younger age groups.

ABRAMSON.

Friedland, C., and Sodi Pallares, D.: On the Significance of an M-Shaped Complex in the Precordial Leads V_1 and V_2 . Arch. Inst. cardiol. México 27:293 (June), 1947.

The authors studied eighty tracings with an M-shaped ventricular complex in Leads V_1 and V_2 . In all of them, the duration of the intrinsic deflection was measured from the beginning of QRS to the vertex or the origin of the descending branch of R.¹ Roentgenograms of most cases and physical examination and necropsy of a few also were studied.

Nearly all tracings were recorded in patients with heart disease. Tracings with an M-complex in Leads V_1 and V_2 should be considered abnormal if other electrical abnormalities are present; otherwise, they should be considered as border line electrocardiograms. If the tracing is recognized as abnormal, there is a 72.5 per cent probability that it is connected with hypertrophy of the right ventricle, with or without simultaneous hypertrophy of the left. If the S wave has an amplitude of 4.5 mm. or more, hypertrophy of both ventricles is probable, though this conclusion requires the presence of other electrocardiographic abnormalities.

LUISADA.

Garcia Ramos, J., and Rosenblueth, S.: Studies on Flutter and Fibrillation. III: The Self-Sustained Activity in the Isolated Auricular Muscle of Mammals. Arch. Inst. cardiol. México 27:302 (June), 1947.

A preparation of auricular myocardium with normal blood supply was obtained by crushing a narrow band around the base of the right auricular appendage in dogs and cats. The activity of the appendage then becomes independent from that of the rest of the auricle. Normal auricular tissue does not contract spontaneously. However, it may discharge impulses for several seconds

or minutes after injections of acetylcholine, adrenaline, or calcium chloride, and after application of stimuli at an appropriate rate. Different types of stimuli cause rapid automatic activity or slow automatic discharges over several seconds or minutes. The study deals mainly with the slow automatic activity.

The electrical phenomena of the isolated auricular appendage were recorded monophasically. Initiation of the propagated impulses usually was preceded by local negativity. However, Bozler's suggestion that spontaneous impulses are initiated by local potentials at the site of origin did not seem to be confirmed, as the impulses did not occur after a constantly fixed degree of local negativity.

Although the isolated auricular myocardium has no apparent automatism when separated from the sinoauricular node, it is potentially able to beat automatically, as shown by the fact that several stimuli are necessary to initiate the activity. The automatism of auricular myocardium resembles that of nodal tissues; it is accelerated by adrenaline, it is inhibited by acetylcholine and potassium ions, and may present a compensatory pause after a premature contraction.

A detailed study of the effects of adrenaline and acetylcholine is presented.

LUISADA.

Robles, C., and Benavides, P. H.: Considerations on Surgical Treatment of Essential Hypertension by Dorso-Lumbar Sympathectomy. Arch. Inst. cardiol. México 27:408 (June), 1947.

The authors present some considerations on the possibilities of the Smithwick operation in hypertensive patients with advanced cardiac failure who do not respond to medical treatment. The history of five cases is reported. All patients reported were improved by the operation so far as heart failure was concerned; all showed a decrease in blood pressure. The response to medical treatment was good after surgery. The authors consider, therefore, that cardiac failure does not represent an absolute contraindication to sympathetic surgery. The conclusions are not absolute, however, because of the brief period of follow-up of the cases (one to two years).

LUISADA.

Marcuse, Peter M.: Nonspecific Myocarditis. Arch. Path. 43:602 (June), 1947.

Marcuse collected thirty-six cases of myocarditis from a total of 3,800 autopsies, the diagnosis being made on microscopic examination of routine sections of heart muscle. Most of these cases showed extensive diffuse or focal myocarditis. Myocardial lesions of known etiology were excluded from this group, as were all cases serologically positive for syphilis. The majority were men less than 40 years of age.

The only gross change was cardiac hypertrophy, which was noted in fifteen cases (43 per cent); an occasional case showed grayish discoloration of the myocardium. The diagnostic microscopic changes were: (1) interstitial leucocytic infiltration, often perivascular; and (2) a secondary parenchymal destruction. Marcuse states that the only constant microscopic feature was the presence of elongated cells with large distorted nuclei, "different from the myocyte of Auitschkow and from Aschoff cells." They were not from degenerating muscle fibers, but probably were endothelial cells.

Practically all of these cases showed extracardiac inflammatory lesions, especially in the lungs. Bronchopneumonia and interstitial pneumonitis were the most commonly associated pulmonary lesions.

Clinical manifestations of cardiac involvement were vague; however, from a pathologic standpoint the incidence of "nonspecific myocarditis" is greater than generally assumed.

GOULEY.

Wilson, R. H., Mortarotti, T. G., and DeEds, F.: **Some Pharmacological Properties of Rutin.** *J. Pharmacol. & Exper. Therap.* 90:120 (June), 1947.

Rutin, placed in the perfusion fluid surrounding excised segments of guinea-pig colon, was capable of prolonging the relaxation produced by epinephrine. The degree of prolongation was proportional to the dose of rutin. If given intraperitoneally in guinea pigs ten to thirty minutes prior to 50 per cent of the lethal dose of histamine, the mortality was reduced. Simultaneous administration of the two drugs showed no protection. In guinea pigs rendered scorbutic, the authors could demonstrate no significant difference in the animals' tendency to develop petechial hemorrhages in those given rutin and in those not given rutin. Therefore, the capillary permeability protective power of rutin could not be confirmed.

GODFREY.

Meyer, O.: **The Ambulatory Treatment of Phlebitis, Thrombophlebitis and Thrombosis With Compression Bandages.** *Surgery* 21:843 (June), 1947.

The author advocates the use of compression bandages in the treatment of venous thrombosis and in the prevention of pulmonary embolism. He uses the combination of a medicated contura bandage applied loosely and a 3-inch-wide pressoplast bandage which is applied over it with strong nonconstricting pressure. The foot, leg, and thigh are covered but the knee as a rule remains free. The patient is then advised to walk as much as possible and to avoid standing.

According to the author, the application of the bandages, using the optimal degree of pressure, will cause immediate relief of pain and rapid reduction in edema in the acute stage of deep thrombophlebitis. He presents statistical studies of others to support the view that with the use of compression bandages, pulmonary embolism is practically prevented. He also points out that the treatment must be supplemented by the removal of primary foci in the oral cavity and secondary foci in the jugular veins, to prevent reinfection of the veins of the leg.

ABRAMSON.

Hinchey, J. J., Hines, E. A., and Ghormely, R. K.: **Osteoporosis Occurring During Potassium Thiocyanate Therapy for Hypertensive Disease.** *Proc. Staff Meet., Mayo Clin.* 22:275 (July 9), 1947.

The authors studied the records of 360 patients with hypertension to whom potassium thiocyanate had been given. Unexplained osteoporosis involving one or more extremities occurred in seven of these patients (2 per cent). A history of trauma or injury at onset was not present. Unexplained osteoporosis was not noted in the group of patients with hypertension who were not receiving potassium thiocyanate.

The average age of this group was 57 years. The dosage of the drug varied considerably during the course of treatment, but was usually in the range of 6 to 9 grains (0.4 to 0.6 Gm.) daily. The onset of symptoms associated with the osteoporosis generally occurred in from three to six months after the patient started taking the drug. They consisted of pain on use of the extremity and subsequent mild swelling of the joint or joints involved. Roentgenograms revealed mild to marked diffuse osteoporosis.

Active therapeutic measures directed toward the osteoporosis were carried out in seven cases while thiocyanate therapy was being continued. The symptoms continued to progress despite these measures in six cases. Slight improvement over a period of several months was noted in the seventh case and this was accelerated when the use of potassium thiocyanate was stopped. Cessation of treatment with potassium thiocyanate was followed by relief in every one of the seven cases whether or not specific measures of treatment of the osteoporosis were used. Use of the drug was resumed in four instances. In two neither the symptoms nor the osteoporosis recurred. Symptoms did recur in the other two and were again relieved when administration of thiocyanate was once more discontinued.

BELLET.

American Heart Association, Inc.

1790 BROADWAY, NEW YORK 19, N. Y.

Telephone Circle 5-8000

THE AMERICAN HEART ASSOCIATION PREPARES FOR INTENSIFIED EDUCATIONAL AND FUND- RAISING ACTIVITIES

Second National Heart Week, Feb. 8, 1948.—In the period that has elapsed since the first observance of National Heart Week last February, the American Heart Association has taken a major step forward in achieving public recognition and greater understanding of the heart diseases through its educational program. A continual stream of information has been released through the media of press and radio to publicize the three-point program of the Association: national research, public and professional education, and community service through the formation and activities of local heart associations.

The groundwork has been well laid for the development of a more comprehensive fund-raising and public relations program during the 1948 observance of National Heart Week, February 8-14. For the first time, a direct appeal will be made to the public for funds. As part of the fund-raising program, an integrated special gifts campaign will be conducted.

The full cooperation of national wire services, national magazines, and radio networks has been assured for the second annual Heart Week. Interest evidenced so far indicates that the observance will surpass the highly effective results achieved last year.

Following last year's procedure, Heart Week programs will be developed which can be coordinated with local heart associations, with the necessary community organization. In addition, it is planned to make a comprehensive drive among Community Chests to obtain their acceptance of the obligation of meeting a community quota for the attack against the heart diseases.

In order to bring the American Heart Association's educational campaign to many communities throughout the United States where there are no local heart associations, cooperation is expected again this year from the United States Junior Chamber of Commerce, the American Legion, Rotary International, and Kiwanis International.

The business and professional women's clubs of New York State will conduct fund-raising activities for the American Heart Association with the support of their sixty community organizations.

To assist these groups with their educational and fund-raising programs the American Heart Association will make available a plastic heart-shaped collection box created by the eminent designer, Stanley Chamberlain; a publicity kit consisting of suggested news releases, editorials, and radio scripts; educational pamphlets and leaflets; a series of three posters dramatizing the story of heart disease and rheumatic fever; a film on heart disease as it affects the average businessman and his family; and a film strip on rheumatic fever.

The nation's leading chain drugstores have agreed to display the plastic heart on counters throughout the United States. It will be mounted on a counter card bearing the legend, "Open Your Heart . . . Give to Fight the Heart Diseases, America's Number One Killer."

Independent druggists and other groups are also cooperating in utilizing the plastic heart.

Creation of Local Heart Associations.—Of equal importance with the fund-raising program is the campaign for the creation of additional local heart associations throughout the United States. In the last analysis, the financial stability of the American Heart Association will depend on the structure and number of local affiliates.

In response to numerous requests received by the American Heart Association for assistance in the formation of local heart associations and in the development of local programs, "A Guide to the Formation of Local Affiliates of the American Heart Association" was recently published. The aim of this booklet is to suggest basic procedures and indicate solutions to many of the problems which arise in the formation of affiliated associations.

In an introduction to the Guide, Dr. A. R. Barnes, president of the Association, points out that vital research in diseases of the heart and circulation has lagged far behind minimum requirements because of lack of community support. "Community cardiovascular programs have only recently begun to emerge," Dr. Barnes says, "and these have been too few in number to meet the overall needs of the public."

Emphasizing further the need and place of the local heart associations, Dr. Barnes says:

"The American Heart Association provides a comprehensive program to deal with the broad aspects of diseases of the heart and blood vessels. The ultimate success of this program depends on an effective organization of local heart associations.

"The local heart association is the task force in this struggle. This has been demonstrated adequately in those areas where strong local heart associations already exist. There is need for similar strong organizations in every important community. These must be active and show initiative in meeting problems peculiar to their individual areas.

"As to the national agency, the American Heart Association is organized to guide and integrate the functions of the local associations, and to serve as a clearing house for their activities. But it is the local heart associations which must do the field work. Through their efforts it will be possible to bring the benefits of scientific research in cardiovascular disease to every citizen in every community in the United States."

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

The Chairman of the Program Committee for the Annual Scientific Session is Dr. Herrman L. Blumgart, 330 Brookline Avenue, Boston, Massachusetts. All who desire to present papers at the meetings in Chicago on June 18 and 19 should forward to Dr. Blumgart an abstract of the proposed presentation of not more than 500 words. The dead line for the receipt of abstracts is Feb. 1, 1948.

AMERICAN HEART JOURNAL

For the Study of the
CIRCULATION



©Am. Ht. Assn.

PUBLISHED MONTHLY

Under the Editorial Direction of
THE AMERICAN HEART ASSOCIATION

THOMAS M. McMILLAN
Editor-in-Chief

ASSOCIATE EDITORS

WALLACE M. YATER
SAMUEL BELLET
LOUIS B. LAPLACE

EDITORIAL BOARD

EDGAR V. ALLEN
ALFRED BLALOCK
CLARENCE E. DE LA CHAPELLE
HARRY GOLDBLATT
TINSLEY R. HARRISON
T. DUCKETT JONES
LOUIS N. KATZ
EUGENE M. LANDIS
JOHN K. LEWIS

H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
HELEN B. TAUSSIG
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

VOLUME 34
JULY-DECEMBER, 1947

ST. LOUIS
THE C. V. MOSBY COMPANY
1947

COPYRIGHT 1947, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in the
United States of America

*Press of
The C. V. Mosby Company
St. Louis*

INDEX TO VOLUME 33

AUTHORS INDEX

A

- ABBOTT, K. H. (See Craig and Abbott), 773*
- ABRAMSON, D. I. (See Shumacker, Jr., and Abramson), 463*
- ACEVES, SALVADOR, AND CARRAL, RAFAEL. The diagnosis of tricuspid valve disease, 114
- ADDARI, F., DE CAROLIS, D., MONTEVECCHI, M., FOSCARINI, M., CURTI, A., SITA, A., ALTANTA, G., JOSONNI, D., RIZZO, S., TAVOSCHI, F., MAGORO, G., AND GRANDI, F. Clinical and experimental studies of sympathomimetic compounds (Sympatol, Veritol, Sympamina), 464*
- ADOLPH, WILLIAM. (See Winsor, Adolph, Ralston, and Leiby), 80
- ALES, J. M. (See Jimenez-Diaz, Arjona, Ales, Grande, Lopez Garcia, and Oya), 294*
- ALLEN, C. R. (See Slocum, Hoefflich, and Allen), 775*
- ALLEN, E. V. The clinical use of anticoagulants, 771*
- ALTANTA, G. (See Addari, de Carolis, Montevicchi, Foscarini, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- ALTSCHUL, RUDOLF. Experimental cholesterol arteriosclerosis, 147*
- ALTSCHULE, M. D. (See Freedberg, McManus, and Altschule), 249
- ALTURE-WERBER, E. (See Loewe and Altüre-Werber), 291*
- ALVAREZ MENA, S. The normal esophageal electrocardiograms, 293*
- ALZAMORA CASTRO, V. Observations on the significance of changes of the S-T segment and the T wave, 293*
- ANNITTO, J. E. (See Chesley and Annitto), 918*
- . (See Chesley, Annitto, and Jarvis), 924*
- ANREP, G. V., BARSOUM, G. S., KENAWY, AND MISRAHY, G. Ammi visnaga in the treatment of the anginal syndrome, 758*
- , KENAWY, M. R., AND MISRAHY, G. Therapeutic uses of khellin, 613*
- ARJONA, E. (See Jimenez-Diaz, Arjona, Ales, Grande, Lopez Garcia, and Oya), 294*
- ASHMAN, RICHARD. (See Gouaux and Ashman), 366
- ASHWORTH, H., AND JONES, A. M. Aneurysmal dilatation of the left auricle with erosion of the spine, 760*

- AUERBACH, STEWART H., AND HARPER, HARRY T., JR. Congenital pulmonary stenosis with closed interventricular septum, 131

B

- BAKER, L. A., AND MUSGRAVE, D. A study of mitral stenosis in patients who survived the age of fifty, 928*
- . (See McNamara, Baker, and Costich), 288
- BARDEN, R. P. (See Pendergrass, Griffith, Jr., Padis, and Barden), 612*
- BARKER, N. W. (See Parker and Barker), 923*
- BARNETT, ROY N., AND ZIMMERMAN, S. L. Coronary arteritis with fatal thrombosis due to *Salmonella choleraesuis* variety Kunzendorf, 441
- BARSOUM, G. S. (See Anrep, Barsoum, Kenawy, and Misrahy), 613*
- . (See Anrep, Barsoum, Kenawy, and Misrahy), 758*
- BARTHOLOMEW, R. A. The possible etiologic significance of thrombosis of a placental vein on the mechanism of placental infarction and associated toxemia of pregnancy, 922*
- BATT, R. C. A roentgenkymographic study of the heart in myasthenia gravis, 461*
- BATTERMAN, ROBERT C., AND DEGRAFF, ARTHUR C. Comparative study on use of purified digitalis glycosides, digoxin, digitoxin, and lanatoside C, for the management of ambulatory patients with congestive heart failure, 663
- BAUERSFELD, S. R. Dissecting aneurysm of the aorta, 928*
- BEAN, W. B. (See Eichna, Horvath, and Bean), 774*
- BEARD, OWEN W., AND DECHERD, GEORGE M., JR. Variations in the first heart sound in complete A-V block, 809
- BELL, F. K., CARR, C. J., AND KRANTZ, J. C. Digitalis. V. The Baljet reaction and pharmacodynamics of diginin, 622*
- BENAVIDES, P. H. (See Robles and Benavides), 931*
- BERCONSKY, I. (See Cossio and Berconsky), 621*
- BERDEZ, G. L. (See Cook, Smith, Giesen, and Berdez), 777*
- BERRY, R. E. L. (See Collier, Campbell, Berry, Sutler, Lyons, and Moe), 929*
- BERRY, R. L. (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick), 295*

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

- BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR. Physiological studies in congenital heart disease. II. Results of pre-operative studies in patients with tetralogy of Fallot, 615*
- BIÖRCK, G. Five cases with pre-excitation electrocardiograms, 146*
- BIÖRCK, G. (See Nylin and Biörck), 916*
- BIRCHALL, R., TAYLOR, R. D., LOWENSTEIN, V. E., AND PAGE, I. H. Clinical studies of the pharmacologic effects of tetraethyl ammonium chloride in hypertensive persons made in an attempt to select patients suitable for lumbar sympathectomy and ganglionectomy, 771*
- BISHOP, L. F. (See Weintraub and Bishop), 925*
- BISHOP, LOUIS F., JR. (See Weintraub and Bishop, Jr.), 284
- BLAND, E. F. (See Castleman and Bland), 148*
- BLONDHEIM, SOLOMON HILLEL. The technique of fetal electrocardiography, 35
- BLOOMFIELD, R. A., LAUSON, H. D., COURNAND, A., BREED, E. S., AND RICHARDS, D. W., JR. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease, 776*
- BLUMBERG, N., AND SCHLOSS, E. M. The effect of circulatory factors on the bromsulphalein test in liver disease, 622*
- BOHNE, W. (See Ratliff, Nesbit, Plumb, and Bohne), 456
- BOONE, B. R., CHAMBERLAIN, W. EDWARD, GILICK, F. G., HENNY, G. C., AND OPPENHEIMER, M. J. Interpreting the electrokymogram of heart and great vessel motion, 560
- BOYLE, MARGARET N., WÉGRIA, RENÉ, CATHCART, RICHARD T., NICKERSON, JOHN L., AND LEVY, ROBERT L. Effects of intravenous injection of nicotine on the circulation, 65
- BRAMS, W. (See Grossman, Feldman, Katz, and Brams), 592
- BRANNON, E. S. (See Nickerson, Warren, and Brannon), 619*
- BRAUN, K., ROTH, I., AND SUESSKIND, S. Intra-ventricular block in malnutrition and vitamin B deficiency, 297*
- BREDA, R., AND COSTA, F. Right-sided ectatic aorta, 761*
- BREID, E. S. (See Bloomfield, Lauson, Cournand, Breed, and Richards, Jr.), 776*
- BREITWIESER, E. R. Electrocardiographic observations in chronic cholecystitis before and after surgery, 771*
- BRENES, M. (See Salazar Mellen, Lozano Lube, and Brenes), 767*
- BRICK, IRVING B., AND GREENFIELD, MAURICE. Reticulum cell sarcoma with cardiac metastasis, 509
- BRIDGES, W. C. (See Wheeler, Bridges, and White), 149*
- BROCH, O. The electrocardiogram in derangements of the organism's water and electrolyte metabolism, 146*
- BRODIE, O. J. (See Walton and Brodie), 773*
- BROWN, A. B. (See Mylks, Brown, and Robinson), 768*
- BROWN, CHESTER R. (See Greisman, Brown, and Smetana), 447
- BROWN, EDWARD E. Diseases associated with low capillary resistance, 241
- BROWN, ELLEN, SAMPSON, JOHN J., WHEELER, EDWIN O., GUNDELFINGER, BENJAMIN F., AND GIANIRACUSA, JOSEPH E. Physiologic changes in the circulation during and after obstetric labor, 311
- BROWN, N. WORTH. (See Means and Brown), 262
- BRUNER, H. D., AND SCHMIDT, CARL F. Blood flow in the bronchial artery of the anesthetized dog, 919*
- BRYANT, J. MARION, AND WOOD, J. EDWIN, JR. Tobacco angina, 20
- BUNTING, H. (See Seldin, Kaplan, and Bunting), 462*
- BURCHELL, HOWARD B., AND CLAGGETT, O. THERON. The clinical syndrome associated with pulmonary arteriovenous fistulas including a case report of a surgical cure, 151
- BURKE, P. J. Penicillin prophylaxis in acute rheumatism, 297*
- BUSHONG, B. B. Traumatic rupture of the aortic valve, 145*
- BUTT, H. R. (See Dry, Butt, and Scheifley), 301*

C

- CAMERON, D. E. Increased reactivity caused by adrenalin, 295*
- CAMPBELL, K. N. (See Collier, Campbell, Berry, Sutler, Lyons, and Moe), 929*
- . (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick), 295*
- CAMPBELL, M. Dissecting aneurysm with survival for three months after rupture into the pleura, 759*
- CARLGRÉN, L. E. Gallop rhythm in children studied by means of calibrated phonocardiography, 465*
- CARLOTTI, JACQUES, COHEN, MANDEL E., AND WHITE, PAUL D. The heart size in neurocirculatory asthenia, effort syndrome, or anxiety neurosis, 552
- DE CAROLIS, D. (See Addari, Montevicchi, Foscarini, Curti, Sita, Altanta, Jossoni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- CARR, C. J. (See Bell, Carr, and Krantz), 622*
- CARRAL, RAFAEL. (See Aceves and Carral), 114
- CARROLL, DOUGLAS, AND CUMMINS, SAMUEL D. Double rupture of the heart following myocardial infarction, 894
- CASE, D. (See Erganian, Forbes, and Case), 297*
- CASMAN, J. Radiographic demonstration of the increase in heart volume after ingestion of a liter of water, 921*

- CASTELLANOS, A., PEREZ DE LOS REYES, R., AND GARCIA LOPEZ, A. Angiocardiography — comparative study with autopsy findings, 621*
- CASTLEMAN, B., AND BLAND, E. F. Organized emboli of the tertiary pulmonary arteries, 148*
- CASTRO, V. A., AND RUBIO, CARLOS W. Significado de algunas alteraciones de las ondas T, 764*
- CATHCART, RICHARD T. (See Boyle, Wégria, Cathcart, Nickerson, and Levy), 65
- CHAMBERLAIN, W. EDWARD. (See Boone, Chamberlain, Gillick, Henny, and Oppenheimer), 560
- CHAMBERS, W. N. Blood pressure studies in 100 cases of coronary occlusion with myocardial infarction, 298*
- CHAPMAN, WILLIAM P. (See White, Cohen, and Chapman), 390
- CHESLEY, L. C., AND ANNITTO, J. E. Pregnancy in the patient with hypertensive disease, 918*
- , —, AND JARVIS, D. G. A study of the inter-action of pregnancy and hypertensive disease, 924*
- CHIODI, H. (See Taquini, Fasciolo, Suarez, and Chiodi), 50
- CHRISTENSEN, B. C. Studies on hyperventilation. II. Electrocardiographic changes in normal man during voluntary hyperventilation, 760*
- CLAGETT, O. THERON. (See Burchell and Clagett), 151
- . (See Deterling, Jr., and Clagett), 471
- CLARK, J. H., NELSON, W., LYONS, C., MAYERSON, H. S., AND DE CAMP, P. Chronic shock: the problem of reduced blood volume in the chronically ill patient. 926*
- CLARK, T. E. (See Kissane, Fidler, and Clark), 622*
- COHEN, MANDEL E. (See Carlotti, Cohen, and White), 552
- . (See White, Cohen, and Chapman), 390
- COLLER, F. A., CAMPBELL, K. N., BERRY, R. E. L., SUTLER, M. R., LYONS, R. H., AND MOE, G. K. Tetra-ethyl-ammonium as an adjunct in the treatment of peripheral vascular disease, and other painful states, 929*
- COLLINS, C. G., NELSON, E. W., JONES, J. R., WEINSTEIN, B. B., AND THOMAS, E. P. Ligation of the vena cava, 456*
- COLLINS, V. J., FOSTER, W. L., AND WEST, W. J. Vasomotor disturbances in poliomyelitis with special reference to treatment with paravertebral sympathetic block, 770*
- COOK, C. D., SMITH, H. L., GIESEN, C. W., AND BERDEZ, G. L. Xanthoma tuberosum, aortic stenosis, coronary sclerosis, and angina pectoris, 777*
- COPLEY, A. L., AND STEFKO, P. L. Coagulation thrombi in segments of artery and vein in dogs and the genesis of thromboembolism, 769*
- CORCORAN, A. C. (See Taylor, Corcoran, and Page), 468*
- COSSIO, P., AND BERCONSKY, I. Acute benign pericarditis, 621*
- COSTA, F. (See Breda and Costa), 761*
- COSTICH, KENNETH. (See McNamara, Baker, and Costich), 288
- COURNAND, A., HIMMELSTEIN, A., RILEY, R. L., AND LESTER, C. W. A follow-up study of the cardiopulmonary function in four young individuals after pneumonectomy, 616*
- . (See Bloomfield, Lauson, Cournand, Breed, and Richards, Jr.), 776*
- CRAFOORD, C. (See Welin, Hamberger, and Crafoord), 463*
- CRAIG, W. M., AND ABBOTT, K. H. Surgical considerations in the treatment of hypertension, 773*
- CRAWFORD, J. HAMILTON, AND DI GREGORIO, N. J. Complete heart block in younger age groups, 540
- CUMMINS, SAMUEL D. (See Carroll and Cummins), 894
- CURTI, A. (See Addari, de Carolis, Montevicchi, Foscari, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*

D

- DACK, S., AND MOLOSHOK, R. Cardiac manifestations of toxic action of emetine hydrochloride in amebic dysentery, 291*
- DAHL-IVERSON, E. (See Espersen and Dahl-Iverson), 913*
- DAVIS, E. Mitral stenosis and pulmonary tuberculosis, 773*
- DAVIS, L., AND PERRET, G. Cerebral thromboangiitis obliterans, 763*
- DAVIS, M. E., AND WORTMANN, R. F. Subacute bacterial endocarditis during pregnancy, 924*
- DAWES, G. S. L. Studies on veratrum alkaloids. VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridine, 769*
- DE CAMP, P. (See Clark, Nelson, Lyons, Mayerson, and De Camp), 926*
- DECHERD, G. M. (See Ruskin and Decherd), 296*
- DECHERD, GEORGE M., JR. (See Beard and Decherd, Jr.), 809
- DEEDS, F. (See Wilson, Mortarotti, and DeEds), 932*
- DEGRAFF, ARTHUR C. (See Batterman and DeGraff), 663
- DEKAMAS, D. (See Proger and Dekamas), 143*
- DELAUNOIS, A. L. (See Heymans and Delaunais), 618*
- DESCHAMPS, P. N. A case of prolonged flutter, 458*
- DETERLING, RALPH A., JR., AND CLAGETT, O. THERON. Aneurysm of the pulmonary artery: review of the literature and report of a case, 471
- DI GREGORIO, N. J. (See Crawford and Di Gregorio), 540

- DiPALMA, J. R. (See Gubner, DiPalma, and Moore), 298*
- DJIN-YÜAN GUO. Dissecting aneurysm of the aorta related to trauma, 916*
- DOWLING, H. F. (See Hirsch, Rotman-Kavka, Dowling, and Sweet), 622*
- DOWNING, M. E. Blood pressure of normal girls from three to sixteen years of age, 777*
- DRAKE, E. H. (See Teplich and Drake), 459*
- DRESSLER, WILLIAM, AND ROESLER, HUGO. High T waves in the earliest stage of myocardial infarction, 627
— (See Roesler and Dressler), 817
- DREYFUSS, F. An observation concerning the hands of patients with rheumatic fever, 762*
- DRISCOLL, R. E. (See Stein and Driscoll), 926*
- DRY, T. J., BUTT, H. R., AND SCHEIFLEY, C. H. The effect of oral administration of para-aminobenzoic acid on the concentration of salicylates in the blood, 301*
- , EDWARDS, J. E., MAYNARD, A. E., MOE, A. E., AND VIGRAN, I. M. Mycotic aneurysm of the posterior tibial artery complicating subacute bacterial endocarditis: antemortem diagnosis is confirmed by instrumental means, 764*
- DUFFAU, G., AND SEPULVEDA, M. Rheumatic nodules in children, 294*
- DUMKE, PAUL R. (See Wexler, Whittenberger, and Dumke), 163
- DUNGAL, NIELS. Cardioaortitis, 457*

E

- ECKENHOFF, J. E., HAFKENSCHIEL, J. H., AND LANDMESSER, C. M. The coronary circulation in the dog, 919*
- ECKSTEIN, R. W., WIGGERS, C. J., AND GRAHAM, G. R. Phasic changes in inferior cava flow of intravascular origin, 920*
- EDEIKEN, JOSEPH. (See Steiger and Edeiken), 674
- EDWARDS, J. E. (See Dry, Edwards, Maynard, Moe, and Vigran), 764
- EIBER, DONALD. (See Feil, Green, and Eiber), 334
- EIBER, HAROLD B. (See Loewe and Eiber), 349
- EICHNA, L. W., HORVATH, S. M., AND BEAN, W. B. Post-exertional orthostatic hypotension, 774*
- ELKELES, A. Disseminated ossified nodules in the lungs associated with mitral stenosis, 774*
- ELMQUIST, A., AND LILJESTRAND, A. On the chemical evaluation of digitalis with the Baljet reaction, 914*
- EPSTEIN, B. S. Rheumatic mitral valve disease without cardiac enlargement, 617*
- EPSTEIN, SAMUEL. Observations on beriberi heart disease, 432
- ERGANIAN, J. A., FORBES, G., AND CASE, D. Salicylate intoxication in the infant and young child, 297*

- ESPERSEN, T., AND DAHL-IVERSEN, E. The clinical picture and treatment of pheochromocytomas of the suprarenal, 913*
- , AND JORGENSEN, J. Electrocardiographic changes in paroxysmal hypertension due to chromaffin adrenal tumor, 916*

F

- FASCILOLO, J. C. (See Taquini, Fasciolo, Suarez, and Chiodi), 50
- FASTIER, F. N., AND SMIRK, F. H. Circulatory properties of iso-thioureas, guanidines, iso-ureas, and amidines, 613*
- FEIL, HAROLD, GREEN, HAROLD D., AND EIBER, DONALD. Voluntary acceleration of heart in a subject showing the Wolff-Parkinson-White syndrome, 334
— (See Weisberger and Feil), 871
- FELDMAN, D. (See Grossman, Feldman, Katz, and Brams), 592
- FIDLER, R. S. (See Kissane, Fidler, and Clark), 622*
- FLEMING, ALLAN J. (See Foulger, Smith, Jr., and Fleming), 507
- FLETCHER, D. E. *Bacillus coli* endocarditis, 743
- FORBES, G. (See Erganian, Forbes, and Case), 297*
- FOREMAN, ROBERT C. (See Opdyke and Foreman), 920*
- FOSCARINI, M. (See Addari, de Carolis, Montevicchi, Foscarini, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- FOSTER, W. L. (See Collins, Foster, and West), 770*
- FOULGER, JOHN H., SMITH, PAUL E., JR., AND FLEMING, ALLAN J. Changes in cardiac vibrational intensity in response to physiologic stress, 507
- FREEDBERG, A. S., McMANUS, M. J., AND ALTSCHULE, M. D. The electrocardiogram in man during an episode of chill and fever induced by intra venous typhoid vaccine, 249
- FREEMAN, N. E. Direct measurement of blood pressure within arterial aneurysms and arteriovenous fistulas, 927*
- (See Hodges and Freeman), 300*
- FRIEDLAND, C., AND SODI PALLARES, D. On the significance of an M-shaped complex in the precordial Leads V₁ and V₂, 930*
- FRIEDMAN, N. B., LANGE, K., AND WEINER, D. The pathology of experimental frostbite, 299*

G

- GARCIA LOPEZ, A. (See Castellanos, Perez De Los Reyes, and Garcia Lopez), 621*
- GARCIA RAMOS, J., AND ROSENBLUETH, S. Studies on flutter and fibrillation. III. The self-sustained activity in the isolated auricular muscle of mammals, 930*
- GATCH, W. D. (See Muntz, Ritchie, and Gatch), 144

- GENDEL, BENJAMIN R. Paroxysmal auricular tachycardia of unusual type, 722
- GEREMIA, A. E. (See Levine and Geremia), 623*
- GERTLER, M. M., AND YOHAELEM, S. B. The effect of atabrine on auricular fibrillation and supraventricular tachycardia in man, 302
- . (See Terroux, Gertler, and Hoff), 461*
- GHORMELY, R. K. (See Hinchey, Hines, and Ghormely), 932*
- GIANSIRACUSA, JOSEPH E. (See Brown, Sampson, Wheeler, Gundelfinger, and Giansiracusa), 311
- GIBSON, W. C. (See Kelly, Gibson, and Meakins), 923*
- GIESEN, C. W. (See Cook, Smith, Giesen, and Berdez), 777*
- GILICK, F. G. (See Boone, Chamberlain, Gillick, Henny, and Oppenheimer), 560
- GIORDANO, G. (See Puddu, Mussafia, and Giordano), 460*
- GLAUBER, JEROME J. (See Young and Glauber), 272
- GOBAT, P. Y. Variations of the amount of cytochrome-C in the myocardium and in the striated muscle in human pathology, 917*
- GOLDBERGER, EMANUEL. The relations of T_1 and T_2 , 395
- GORE, IRA, AND SAPHIR, OTTO. Myocarditis, 827
- , AND ———. Myocarditis associated with acute nasopharyngitis and acute tonsillitis, 831
- GOUAUX, JAMES L., AND ASHMAN, RICHARD. Auricular fibrillation with aberration simulating ventricular paroxysmal tachycardia, 366
- GOVEA, J. Ayerza's disease, 621*
- GOVIER, W. M., YANZ, N., AND GRELIS, M. E. The effect of a-tocopherol phosphate, digitoxin, and certain compounds related to the latter on cardiac muscle metabolism in vitro, 761*
- GRAHAM, G. R. (See Eckstein, Wiggers, and Graham), 920*
- GRANDE, F. (See Jimenez-Diaz, Arjona, Ales, Grande, Lopez Garcia, and Oya), 294*
- GRANDI, F. (See Addari, de Carolis, Montevicchi, Foscarini, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- GRAY, F. D., JR. (See Bing, Vandam, and Gray, Jr.), 615*
- GRAYSON, CHARLES E. (See Windholz and Grayson), 180
- GREEN, HAROLD D. (See Feil, Green, and Eiber), 334
- GREENFIELD, MAURICE. (See Brick and Greenfield), 599
- GREGERSEN, MANGUS I., AND ROOT, WALTER S. Experimental traumatic shock produced by muscle contusion with a note on the effects of bullet wounds, 465*
- GREISMAN, HARRY, BROWN, CHESTER R., AND SMETANA, HANS. Massive hydropericardium with compression and angulation of the inferior vena cava, 447
- GRELIS, M. E. (See Govier, Yanz, and Grellis), 761*
- GRIFFITH, J. Q., JR. (See Pendergrass, Griffith, Jr., Padis, and Barden), 612*
- GROSSMAN, M., FELDMAN, D., KATZ, L. N., AND BRAMS, W. Treatment of subacute bacterial endocarditis due to organisms highly resistant to penicillin, 592
- GROWN, R. H. (See Hoyne and Grown), 616*
- GUBNER, R., DIPALMA, J. R., AND MOORE, E. Specific dynamic action as a means of augmenting peripheral blood flow; use of aminoacetic acid, 298*
- GUNDELFINGER, BENJAMIN, F. (See Brown, Sampson, Wheeler, Gundelfinger, and Giansiracusa), 311
- GURVICH, N. L., AND YUNIEV, G. S. Restoration of heart rhythm during fibrillation by a condenser discharge, 459*

H

- HAFKENSCHIEL, J. H. (See Eckenhoff, Hafkenschiel, and Landmesser), 919*
- HALL, V. E. (See Kipple, Waldman, and Hall), 769*
- HAMBERGER, C. A. (See Welin, Hamberger, and Crafoord), 463*
- HANDLEY, C. A., AND TELFORD, J. The effect of digitalis on the fluid distribution of the body, 468*
- HARPER, HARRY T., JR. (See Auerbach and Harper, Jr.), 131
- HARRIS, T. N. The failure of massive salicylate therapy to suppress the inflammatory reaction in rheumatic fever, 778*
- HELLERSTEIN, H. K. Endocardial pockets of left atrium, 751
- HENNY, G. C. (See Boone, Chamberlain, Gillick, Henny, and Oppenheimer), 560
- HENSON, M. (See King and Henson), 300*
- HERRMANN, GEORGE R., AND SCHOFIELD, NORMAN D. The syndrome of rupture of aortic root or sinus of Valsalva aneurysm into the right atrium, 87
- HEYMANS, C., AND DELAUNOIS, A. L. The influence of arterial work and pressure on the activity of the cardiovascular and respiratory centers, 618*
- , PANNIER, R., AND VANOSTENDE, A. The influence of pulmonary hyperventilation on the vasomotor reflexes of the carotid sinus and on the tonus of the vasomotor center, 618*
- , ———, AND VERBEKE, R. The influence of the anticholinesterases, prostigmine, eserine and di-isopropylfluorophosphate, and of atropine on the central and peripheral transmission of nervous excitation, 617*
- HIMMELSTEIN, A. (See Cournand, Himmelstein, Riley, and Lester), 616*

- HINCHEY, J. J., HINES, E. A., AND GHORMELY, R. K. Osteoporosis occurring during potassium thiocyanate therapy for hypertensive disease, 932*
- HINES, E. A. (See Hinchey, Hines, and Ghormely), 932*
- HIRATZKA, TOMIHARU. (See Myers, Klein, Stofer, and Hiratzka), 785
- HIRSCH, H. L., ROTMAN-KAVKA, G., DOWLING, H. F., AND SWEE, L. K. Penicillin therapy of scarlet fever, 622*
- HODGES, H. H., AND FREEMAN, N. E. Thrombophlebitis on the medical service of a General Hospital, 300*
- HOEFELICH, E. A. (See Slocum, Hoeflich, and Allen), 775*
- HOFF, H. E. (See Terroux, Gertler, and Hoff), 461*
- HOLMAN, DELAVAN V., AND PIERCE, MILA. Nongangrenous frostbite of the feet, 100
- HOLOUBEK, ALICE BAKER. (See Holoubek and Holoubek), 709
- . (See Holoubek and Holoubek), 715
- HOLOUBEK, JOE E., AND HOLOUBEK, ALICE BAKER. Heart disease in the South. II. A statistical survey of one hundred seventeen deaths due to rheumatic heart disease, 709
- , AND ———. Heart disease in the South. III. An analysis of two hundred seventeen deaths due to arteriosclerotic heart disease, 715
- HONIGMAN, A. H., AND KARNS, J. R. Healed subacute bacterial endocarditis: report of two cases with death due to congestive heart failure, 925*
- HOUBLER, S. W. (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Renick), 295*
- HORVATH, S. M. (See Eichna, Horvath, and Bean), 774*
- HOYNE, A. L., AND GROWN, R. H. Penicillin for scarlet fever, 616*
- HUFNAGEL, C. A. Permanent intubation of the thoracic aorta, 768*
- HUMPHREYS, R. J. (See Raab and Humphreys), 763*
- HUNTER, W. C. (See Young and Hunter), 466*

I

- IRWIN, C. W. (See Solomon and Irwin), 144*

J

- JARVIS, D. G. (See Chesley, Annitto, and Jarvis), 924*
- JIMENEZ-DIAZ, C., ARJONA, E., ALES, J. M., GRANDE, F., LOPEZ GARCIA, E., AND OYA, J. C. The influence of alterations of bloodflow through the lesser circulation upon volume and elasticity of the lungs, 294*
- JOHNSON, A. L., WOLLIN, D. G., AND ROSS, J. B. Heart catheterization in the investigation of congenital heart disease, 457*
- JOEL, E., AND MELZER, L. Rheumatic fever following athletic trauma, 762*

- JONES, A. B. Peripheral venous thrombosis: preventive measures and treatment, 766*
- JONES, A. M. (See Ashworth and Jones), 760*
- JONES, J. R. (See Collins, Nelson, Jones, Weinstein, and Thomas), 456*
- JOSONNI, D. (See Addari, de Carolis, Montevvecchi, Foscarini, Curti, Sita, Al-tanta, Josonni, Rizzo, Tavo-schi, Magoro, and Grandi), 464*

K

- KADISH, ARNOLD H. Coagulation of the blood in lusteroid tubes: a study of normal persons and patients with arterial or venous thrombosis, 212
- . Coagulation time of the blood in lusteroid tubes: a study of patients receiving dicumarol, 225
- KAMINS, MAURICE. (See Uyeyama, Kondo, and Kamins), 580
- KAPLAN, H. S. (See Seldin, Kaplan, and Bunting), 462*
- KARNS, J. R. (See Honigman and Karns), 925*
- KATZ, L. N. (See Grossman, Feldman, Katz, and Brams), 592
- . (See Mack, Langendorf, and Katz), 374
- . (See Wilburne, Surtshin, Rodbard, and Katz), 860
- KELLY, H. G., GIBSON, W. C., AND MEAKINS, J. F. Cerebral air embolism following artificial pneumothorax treatment with prolonged inhalation of oxygen, 923*
- KENAWY. (See Anrep, Barsoum, Kenawy, and Misrahy), 758*
- KENAWY, M. R. (See Anrep, Barsoum, Kenawy, and Misrahy), 613*
- KENDALL, F. E. (See Steiner and Kendall), 296*
- KENNEDY, B. J., AND SEED, JOHN. The treatment of subacute bacterial endocarditis with penicillin in beeswax-peanut oil: gluteal abscesses and rupture of the spleen, 906
- KING, B. G., AND HENSON, M. Electrocardiographic changes in fulminating anoxia, 300*
- KIPPLE, H. M., WALDMAN, M. S., AND HALL, V. E. Cardiovascular effects of sodium caprylate in the cat, 769*
- KIRK, G. D. Ligation of inferior vena cava for septic thrombophlebitis, 772*
- KISSANE, R. W., FIDLER, R. S., AND CLARK, T. E. Liver dysfunction in rheumatic heart disease, 622*
- KLEIN, HOWARD A. (See Myers, Klein, Stofer, and Hiratzka), 785
- KLEMME, R. M. (See Saccomanno, Utgerback, and Klemme), 624*
- KONDO, BENJAMIN. (See Uyeyama, Kondo, and Kamins), 580
- KOSSBERGER, J. Rheumatic pneumonia, 303*
- KOSSMANN, C. E. Relative importance of certain variables in the clinical determination of blood pressure, 292*
- KOTTKE, F. J., KUBICEK, W. G., AND LAKER, D. J. Physical and nervous factors in experimental hypertension, 302*

- KRANTZ, J. C. (See Bell, Carr, and Krantz), 622*
- KRIEGER, V. I., AND WEIDEN, S. The value of the cold pressor test in the prediction of hypertension and toxemia in pregnancy, 921*
- KRONTIRIS, A. Experiences with sympathectomy for sequelae of trench feet, 767*
- KUBICEK, W. G. (See Kottke, Kubicek, and Laker), 302*

L

- LAKER, D. J. (See Kottke, Kubicek, and Laker), 302*
- LANDIS, E. M. (See Sobin and Landis), 918*
- LANDMESSER, C. M. (See Eckenhoff, Hafkenschiel, and Landmesser), 919*
- LANGE, K. (See Friedman, Lange, and Weiner), 299*
- LANGENDORF, R., AND MEHLMAN, J. S. Blocked (nonconducted) A-V nodal premature systoles imitating first and second degree A-V block, 500
- . (See Mack, Langendorf, and Katz), 374
- LAUSON, H. D. (See Bloomfield, Lawson, Courmand, Breed, and Richards, Jr.), 776*
- LEIBY, GEORGE M. (See Winsor, Adolph, Ralston, and Leiby), 80
- LESTER, C. W. (See Courmand, Himmelstein, Riley, and Lester), 616*
- LEVINE, S. A., AND GEREMIA, A. E. Clinical features of patent ductus arteriosus with special reference to cardiac murmurs, 623*
- LEVY, ROBERT L. (See Boyle, Wégria, Cathcart, Nickerson, and Levy), 65
- LIAN, C., AND MINOT, G. Radio-electrokymography, 758*
- , AND MANTOUX, G. Syncope and bundle branch block, 914*
- LIBBRECHT, L. A special form of essential hypertension with paradoxical pharmacodynamic reactions, 917*
- LILJESTRAND, A. (See Elmquist and Liljestrand), 914*
- LINDGREN, A. Cutaneous precordial anaesthesia in angina pectoris and coronary occlusion (an experimental study), 916*
- LINDGREN, E. The roentgen diagnosis of arteriovenous aneurysm of the lung, 145*
- LINDGREN, I. High oxygen concentration under normal and increased respiratory pressure in cardiac pain and in pulmonary edema, 460*
- LIVEZEY, MARY M. (See Wolferth and Livezey), 1
- LOEWE, L., AND ALTURE-WERBER, E. The clinical manifestations of subacute bacterial endocarditis caused by *Streptococcus s.b.e.*, 291*
- LOEWE, LEO, AND EIBER, HAROLD B. Subacute bacterial endocarditis of undetermined etiology, 349
- LOPEZ, GARCIA E. (See Jimenez-Diaz, Arjona, Ales, Grande, Lopez Garcia, and Oya), 294*

- LOUBE, SAMUEL DENNIS. (See Roberts and Loube), 188
- LOWENSTEIN, V. E. (See Birchall, Taylor, Lowenstein, and Page), 771*
- LOZANO LUBE, E. (See Salazar Mellen, Lozano Lube, and Brenes), 767*
- LUPTON, A. M. The effect of perfusion through the isolated liver on the prothrombin activity of blood from normal and dicumarol treated rats, 768*
- LYONS, C. (See Clark, Nelson, Lyons, Mayer-son, and De Camp), 926*
- LYONS, R. H., MOE, G. K., NELIGH, R. B., HOOBLER, S. W., CAMPBELL, K. N., BERRY, R. L., AND RENNICK, B. R. The effects of blockade of the autonomic ganglia in man with tetraethylammonium. Preliminary observations on its clinical application, 295*
- . (See Collier, Campbell, Berry, Sutler, Lyons, and Moe), 929*

M

- MCCABE, EDWARD S. Spontaneous interstitial emphysema of the lung simulating organic heart disease, 729
- McGEE, CHARLES J. (See Priest, Smith and McGee), 765*
- MACHT, D. I. Thromboplastic properties of digitaloids and mercurial diuretics employed in cardiology, 458*
- MACK, I., LANGENDORF, R., AND KATZ, L. N. The supernormal phase of recovery of conduction in the human heart, 374
- McKINLEY, W. FRANK. (See Ruskin and McKinley), 691
- MACLEAN, HELEN. (See Schlichter and MacLean), 209
- McMANUS, M. J. (See Freedberg, McManus, and Altschule), 249
- MACMILLAN, R. L. Adrenal apoplexy associated with hypertension, 458*
- McNAMARA, W. L., BAKER, L. A., AND COSTICH, KENNETH. Asymptomatic congenital anomaly of the heart: congenital muscular cord bridging walls of auricle above center of mitral valve, 288
- MAGORO, G. (See Addari, de Carolis, Montevicchi, Foscarini, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- MAGRO, G. Intraventricular conduction on exercise: a cardiac function test, 465*
- MAHONEY, E. B. (See Morton, Mahoney, and Mider), 773*
- MANTOUX, G. (See Lian and Mantoux), 914*
- MARCHAL, M. The registration of pulsations of the lung parenchyma and the cardiovascular system by Kine-densigraphy, 758*
- MARCUSE, PETER M. Nonspecific myocarditis, 931*
- MARSHALL, F. A. Tetany following mercurial diuresis, 921*
- MARTIN, HELEN EASTMAN, AND WERTMAN, MAXINE. Electrolyte changes and the electrocardiogram in diabetic acidosis, 646

- MAUER, EDGAR, F. On the etiology of clubbing of the fingers, 852
- MAYERSON, H. S. (See Clark, Nelson, Lyons, Mayerson, and De Camp), 926*
- MAYNARD, A. E. (See Dry, Edwards, Maynard, Moe, and Vigran), 764*
- MAYOCK, R. L., AND ROSE, E. Insensitivity to epinephrine in a patient with a functioning tumor of the adrenal medulla, 295*
- MEAKINS, J. F. (See Kelly, Gibson, and Meakins), 923*
- MEANS, MYRON G., AND BROWN, N. WORTH. Secondary hypertrophic osteoarthropathy in congenital heart disease, 262
- MECCHERI, L. A. On the pathological variations of venous pressure, 913*
- MEHLMAN, J. S. (See Langendorf and Mehlman), 500
- MELZER, L. (See Jokl and Melzer), 762*
- MENDEZ, R. General concept of digitalis action, 764*
- MERCHANT IGLESIAS, A. (See Ortiz de Landazuri, Perianes Carro, and Merchante Iglesias), 294*
- MEYER, O. The ambulatory treatment of phlebitis, thrombophlebitis, and thrombosis with compression bandages, 932*
- MEYER, O. O. (See Thill and Meyer), 300*
- MIDDLETON, HARVEY N. Electrocardiographic studies of gunshot and stab wounds of the heart, 899
- MIDER, G. B. (See Morton, Mahoney, and Mider), 773*
- MILLS, P. J. W. Hypertensive headache treated with potassium thiocyanate, 614*
- MINOT, G. (See Lian and Minot), 758*
- MISRAHY, G. (See Anrep, Barsoum, Kenawy, and Misrahy), 613*
- . (See Anrep, Barsoum, Kenawy, and Misrahy), 758*
- MOE, A. E. (See Dry, Edwards, Maynard, Moe, and Vigran), 764*
- MOE, G. K. (See Coller, Campbell, Berry, Suttler, Lyons, and Moe), 929*
- . (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick), 295*
- MOLOSHOK, R. (See Dack and Moloshok), 291*
- MONTEVECCHI, M. (See Addari, de Carolis, Montevicchi, Foscari, Curti, Sita, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- MOORE, E. (See Gubner, DiPalma, and Moore), 298*
- MOORE, FERRALL H., AND SCHOFF, CHARLES. Paroxysmal diaphragmatic flutter with symptoms suggesting coronary thrombosis, 889
- MORTAROTTI, T. G. (See Wilson, Mortarotti, and DeEds), 932*
- MORTON, J. J., MAHONEY, E. B., AND MIDER, G. B. An evaluation of pulmonary embolism following intravascular venous thrombosis, 773*
- MUGICA ECHARTE, J. The functional state of the vascular system in pulmonary tuberculosis. V. The lungs as blood depots, 294*
- MUNTZ, H. H., RITCHIE, J. O., AND GATCH, W. D. Adrenalin producing tumor (pheochromocytoma) containing 2,300 milligrams of adrenalin, 144*
- MUSGRAVE, D. (See Baker and Musgrave), 928*
- MUSSAFIA, A. (See Puddu, Mussafia, and Giordano), 460*
- MYERS, GORDON B., KLEIN, HOWARD A., STOFER, BERT E., AND HIRATZKA, TOMIHARU. Normal variations in multiple precordial leads, 785
- MYLKS, G. W., BROWN, A. B., AND ROBINSON, C. N. Air embolism during labor, 768*

N

- NECHOLES, H. (See Olson and Necholes), 766*
- NELIGH, R. B. (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick), 295*
- NELSON, E. W. (See Collins, Nelson, Jones, Weinstein, and Thomas), 456*
- NELSON, W. (See Clark, Nelson, Lyons, Mayerson, and De Camp), 926*
- NESBIT, R. M. (See Ratliff, Nesbit, Plumb, and Bohne), 456*
- NICKERSON, J. L., WARREN, J. V., AND BRANNON, E. S. The cardiac output in man: studies with the low frequency, critically damped ballistocardiograph, and the method of right atrial catheterization, 619*
- NICKERSON, JOHN L. (See Boyle, Wégria, Cathcart, Nickerson, and Levy), 65
- NISSIM, J. A. Dissecting aneurysm of the aorta: a new sign, 760*
- NORMAN, JAMES K. Reactions to decholin in circulation time determination, 740
- NYLIN, G., AND BIÖRCK, G. Circulatory corpuscle and blood volume in a case of patent ductus arteriosus before and after ligation, 916*
- NYLIN, GUSTAV. Circulatory blood volume of some organs, 174

O

- Odell, L. D. Renal filtration rates in pregnancy toxemia; inulin and exogenous creatinine, 775*
- DE OLIVEIRA, H. R. (See Poppe and de Oliveira), 620*
- OLSON, W. H., AND NECHOLES, H. Studies on anuria: effect of infusion fluids and diuretics on the anuria resulting from severe burns, 766*
- OPDYKE, DAVID F., AND FOREMAN, ROBERT C. A study of coronary flow under conditions of hemorrhagic hypotension and shock, 920*
- OPPENHEIMER, M. J. (See Boone, Chamberlain, Gillick, Henny, and Oppenheimer), 560
- ORTIZ DE LANDAZURI, E., PERIANES CARRO, J., AND MERCHANT IGLESIAS, A. Treatment of subacute bacterial endocarditis with penicillin, 294*
- ORTIZ RAMIREZ, T. Variations of cardiac pain caused by respiration, postural changes, and pressure, 767*

- OVERMAN, R. R. (See Wang, Painter, and Overman), 466*
 OYA, J. C. (See Jimenez-Diaz, Arjona, Ales, Grande, Lopez Garcia, and Oya), 294*

P

- PADIS, N. (See Pendergrass, Griffith, Jr., Padis, and Barden), 612*
 PAGE, I. H. (See Birchall, Taylor, Lowenstein, and Page), 771*
 —. (See Taylor, Corcoran, and Page), 468*
 PAINTER, E. E. (See Wang, Painter, and Overman), 466*
 PANNIER, R. (See Heymans, Pannier, and Vanostende), 618*
 —. (See Heymans, Pannier, and Verbeke), 617*
 PARKER, R. L., AND BARKER, N. W. The use of anticoagulants in the management of acute myocardial infarction, 923*
 PEET, MAX M. Results of bilateral supradiaphragmatic splanchnicectomy for arterial hypertension, 619*
 PENDERGRASS, E. P., GRIFFITH, J. O., JR., PADIS, N., AND BARDEN, R. P. The indications for irradiation of the pituitary gland in patients with arterial hypertension, 612*
 PEREZ DE LOS REYES, R. (See Castellanos, Perez De Los Reyes, and Garcia Lopez), 621*
 PERIANES CARRO, J. (See Oritz de Landazuri, Perianes Carro, and Merchante Iglesias), 294*
 PERRET, G. (See Davis and Perret), 763*
 PIERCE, MILA. (See Holman and Pierce), 100
 PLOTZ, M. Bronchial spasm in cardiac asthma, 462*
 PLUMB, R. T. (See Ratliff, Nesbit, Plumb, and Bohne), 456*
 POLIAKOFF, H. Mild rheumatic reaction in Coast Guard recruits, 298*
 POPPE, J. K., AND DE OLIVEIRA, H. R. Treatment of syphilitic aneurysms by cellophane wrapping, 620*
 POPPEN, J. L. Extensive combined thoracolumbar sympathectomy in hypertension, 775*
 PORTER, W. B. The effect of patent ductus arteriosus on body growth, 299*
 PRATT-THOMAS, H. R. Tuberculous sclerosis with congenital tumors of heart and kidney, 292*
 PRIEST, WALTER S., SMITH, JACQUES M., AND MCGEE, CHARLES J. Penicillin therapy of subacute bacterial endocarditis, 765*
 PROGER, S., AND DEKAMOS, D. Some effects of injected cytochrome C in myocardial and cerebral anoxemia in man, 143*
 PRUCHE, A. Electrocardiograms obtained from precordial positions defined by x-rays, 758*
 PUDDU, V., MUSSAFIA, A., AND GIORDANO, G. An unusual electrocardiographic pattern of myocardial infarction, 460*
 PUGH, D. G. The roentgenologic diagnosis of coarctation of the aorta, 620*

Q

- QUIMBY, E. H. (See Smith and Quimby), 624*
 —. (See Smith and Quimby), 765*

R

- RAAB, W., AND HUMPHREYS, R. J. Drug action upon myocardial epinephrine-sympathin concentration and heart rate (nitroglycerine, papaverine, prisol and dibenamine hydrochloride), 763*
 RALSTON, WALTER. (See Winsor, Adolph, Ralston, and Leiby), 80
 RAMOS, J. GARCIA. (See Rosenblueth and Ramos), 764*
 RATLIFF, R. K., NESBIT, R. M., PLUMB, R. T., AND BOHNE, W. Nephrectomy for hypertension with unilateral renal disease, 456*
 Rauchwerger, S. M., and Rogers, R. J. Tuberculoma of the myocardium, 280
 REES, H. C., AND SLEVIN, J. G. Surgical management of vascular leg ulcers, 923*
 REITMAN, N. The antistreptolysin titer as a diagnostic aid in carditis of obscure etiology, 926*
 RENNICK, B. R. (See Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick), 295*
 RESANO, J. H. Dysphagia caused by aortic aneurysm treated by ligation of the descending thoracic aorta and forward displacement of the esophagus by forming a new hiatus, 293*
 REVENO, W. S. Thiouracil in angina pectoris, 148*
 RICHARDS, D. W., JR. (See Bloomfield, Lauson, Cournand, Breed, and Richards, Jr.), 776*
 RILEY, R. L. (See Cournand, Himmelstein, Riley, and Lester), 616*
 RITCHIE, J. O. (See Muntz, Ritchie, and Gatch), 144
 RIZZO, S. (See Addari, de Carolis, Montevicchi, Foscari, Curti, Sita, Altanta, Josonni, Rizzo, Tavooschi, Magoro, and Grandi), 464*
 ROBBINS, L. L. The technique of the roentgenologic demonstration of pulmonary infarct, 145*
 ROBERTS, JOSEPH THOMAS, AND LOUBE, SAMUEL DENNIS. Congenital single coronary artery in man, 189
 ROBERTSON, THEODORE. Paracolon bacillus endocarditis of the pulmonic valve secondary to infected polycystic kidneys, 766*
 ROBINSON, C. N. (See Mylks, Brown, and Robinson), 768*
 ROBLES, C., AND BENAVIDES, P. H. Considerations on surgical treatment of essential hypertension by dorso-lumbar sympathectomy, 931*
 ROBLES GIL, J. Clinical and histopathological study of the nodules in various rheumatic diseases, 767*
 RODBARD, S. (See Wilburne, Surtshin, Rodbard, and Katz), 860

- ROESLER, HUGO, AND DRESSLER, WILLIAM. An electrocardiographic pattern of infarction of the interventricular septum, extending from the anterior to the posterior aspect of the heart, 817
— (See Dressler and Roesler), 627
- ROGERS, H. M. The cardiovascular manifestations of induced thyrotoxicosis, 929*
- ROGERS, R. J. (See Rauchwerger and Rogers), 280
- ROOT, WALTER S. (See Gregersen and Root), 465*
- ROSE, E. (See Mayock and Rose), 295*
- ROSENBAUM, F. F. Right ventricular and right auricular hypertrophy of obscure origin, 144*
- ROSENBLUETH, A., AND RAMOS, J. GARCIA. Action of artificial obstacles on experimental flutter, 764*
- ROSENBLUETH, S. (See Garcia Ramos and Rosenblueth), 930*
- ROSS, J. B. (See Johnson, Wollin, and Ross), 457*
- ROTH, I. (See Brown, Roth, and Suesskind), 297*
- ROTMAN-KAVKA, G. (See Hirsch, Rotman-Kavka, Dowling, and Sweet), 622*
- RUBIO, CARLOS W. (See Castro and Rubio), 764*
- RUDOLF, JAFFE. Chronic isolated myocarditis, 143*
- RUSHMER, ROBERT F. Circulatory effects of three modifications of the Valsalva experiment, 399
- RUSKIN, A., AND DECHERD, G. M. Thiamine circulation time, 296*
- RUSKIN, ARTHUR, AND MCKINLEY, W. FRANK. Comparative study of potassium thiocyanate and other drugs in the treatment of essential hypertension, 691
— Pitressin test of coronary insufficiency, 569
- RUSSEK, H. I. (See Southworth and Russek), 624*

S

- SACCOMANNO, G., UTGTERBACK, R. A., AND KLEMME, R. M. Anatomic data regarding the surgical treatment of angina pectoris, 624*
- SALAZAR MELLEN, M., LOZANO LUBE, E., AND BRENES, M. A comparative study of cultures of arterial or venous blood and bone marrow in patients with subacute bacterial endocarditis, 767*
- SAMPSON, JOHN J. (See Brown, Sampson, Wheeler, Gundelfinger, and Giansiracusa), 311
- SANADRIA, A. 2-Thiouracil in heart failure and in angina pectoris, 460*
- SAPHIR, OTTO. Myocardial granulomas in subacute bacterial endocarditis, 293*
— (See Gore and Saphir), 827
— (See Gore and Saphir), 831
- SCARLINI, F. Rupture of a chronic fibrous aneurysm on the interventricular septum, 148*
- SCHIFFLEY, C. H. (See Dry, Butt, and Scheiffley), 301*

- SCHERF, D., AND SCHLACHMAN, M. The electrocardiographic changes caused by hyperventilation, 299*
- SCHIROSA, G. (See Turchetti and Schirosa), 776*
- SCHLACHMAN, M. (See Scherf and Schlachman), 299*
- SCHLAMOWITZ, ISADORE. An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. IV. The effect of position change on the relationships of the Q-T and the T-P intervals respectively to the cycle length (R-R interval), 702
— An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. V. The effect of changing heart rate upon Q-T interval and the T-P interval and their respective relationships to the cycle length (R-R interval), 878
- SCHLICHTER, J. G., AND MACLEAN, HELEN. A method of determining the effective therapeutic level in the treatment of subacute bacterial endocarditis with penicillin, 209
- SCHLOSS, E. M. (See Blumberg and Schloss), 622*
- SCHMIDT, CARL F. (See Bruner and Schmidt), 919*
- SCHOFF, CHARLES. (See Moore and Schoff), 889
- SCHOFIELD, NORMAN D. (See Herrmann and Schofield), 87
- SEED, JOHN. (See Kennedy and Seed), 906
- SEGRS, M. The normal and pathological aspects of conduction during the refractory phase, 618*
- SELDIN, D. W., KAPLAN, H. S., AND BUNTING, H. Rheumatic pneumonia, 462*
- SEPULVEDA, M. (See Duffau and Sepulveda), 294*
- SERVELLE, M. Lymphography and elephantiasis, 914*
- SHAFFER, J. O. A method of rapid transfusion into the femoral vessels in patients without adequate peripheral superficial veins, 927*
- Intra-arterial penicillin in the surgical treatment of infections of the extremities, 927*
- SHAFIROFF, B. J. P. Ligation of the inferior vena cava, 772*
- SHICK, R. M. Surgical treatment of coarctation of the aorta, 620*
- SHUMACKER, H. B., JR., AND ABRAMSON, D. I. Sympathectomy in trench foot, 463*
- SIEGAL, S. (See Zeman and Siegal), 772*
- SILVERMAN, JACOB J. Shrapnel wound of the heart with benign manifestations, 419
- SITA, A. (See Addari, de Carolis, Montevocchi, Foscari, Curti, Sita, Altanta, Jossioni, Rizzo, Tavooschi, Magoro, and Grandi), 464*
- SLEVIN, J. G. (See Rees and Slevin), 923*
- SLOCUM, H. C., HOEFELICH, E. A., AND ALLEN, C. R. Circulatory and respiratory distress from extreme positions on the operating table, 775*

- SMETANA, HANS. (*See* Greisman, Brown, and Smetana), 447
- SMIRK, F. H. (*See* Fastier and Smirk), 613*
- SMITH, B. C., AND QUIMBY, E. H. The use of radioactive sodium in the study of peripheral vascular disease, 624*
- AND —. The use of radioactive sodium in the study of peripheral vascular disease, 765*
- SMITH, H. L. (*See* Cook, Smith, Giesen, and Berdez), 777*
- SMITH, JACQUES M. (*See* Priest, Smith, and McGee), 765*
- SMITH, PAUL E., JR. (*See* Foulger, Smith, Jr., and Fleming), 507
- SOBIN, S. S., AND LANDIS, E. M. Blood pressure of the rat during acute and chronic choline deficiency, 918*
- SODI PALLARES, D. (*See* Friedland and Sodi Pallares), 930*
- SOLARZ, SYLVAN D. An electrocardiographic study of one hundred fourteen consecutive cases of trichinosis, 230
- SOLOMON, S., AND IRWIN, C. W. Cutaneous diphtheria with toxic myocarditis, 144*
- SOSSAI, A. On a case of spontaneous rupture of the heart with lung survival; 761*
- SOUTHWORTH, J. L., AND RUSSEK, H. I. A technic for testing hypertensive patients preoperatively, 624*
- STEFKO, P. L. (*See* Copley and Stefko), 769*
- STEIGER, HOWARD P., AND EDEIKEN, JOSEPH. Electrocardiographic changes in early syphilis, 674
- STEIN, M. H., AND DRISCOLL, R. E. Paroxysmal ventricular tachycardia with acute left ventricular failure in a patient with no evidence of organic heart disease, 926*
- STEINER, A., AND KENDALL, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil, 296*
- STOFER, BERT E. (*See* Myers, Klein, Stofer, and Hiratzka), 785
- STUDY, ROBERT S. (*See* Wendkos and Study), 138
- SUAREZ, J. R. E. (*See* Taquini, Fasciolo, Suarez, and Chiodi), 50
- SUESSKIND, S. (*See* Broun, Roth, and Suesskind), 297*
- SURTSHIN, A. (*See* Wilburne, Surtshin, Rodbard, and Katz), 860
- SUTLER, M. R. (*See* Collier, Campbell, Berry, Sutler, Lyons, and Moe), 929*
- SWEE, L. K. (*See* Hirsch, Rotman-Kavka, Dowling, and Sweet), 622*
- T
- TAQUINI, ALBERTO C., FASCILOLO, J. C., SUAREZ, J. R. E., AND CHIODI, H. Circulatory adaptations in Ayerza's syndrome—black cardiacs, 50
- TAVOSCHI, F. (*See* Addari, de Carolis, Montevicchi, Altanta, Josonni, Rizzo, Tavoschi, Magoro, and Grandi), 464*
- TAYLOR, R. D., CORCORAN, A. C., AND PAGE, I. H. Menopausal hypertension, 468*
- (*See* Birchall, Taylor, Lowenstein, and Page), 771*
- TELFORD, J. (*See* Handley and Telford), 468*
- TEPLICH, J. G., AND DRAKE, E. H. The roentgen and cardiac manifestations of funnel chest, 459*
- TERROUX, K. GODWIN, GERTLER, M. M., AND HOFF, H. E. The alkali tolerance of the dog heart, 461*
- THEBOUT, B. R., AND WARD, C. S. Ligation of the inferior vena cava in thromboembolism, 770*
- THILL, C. J., AND MEYER, O. O. Experiences with penicillin and dicumarol in the treatment of subacute bacterial endocarditis, 300*
- THOMAS, E. P. (*See* Collins, Nelson, Jones, Weinstein, and Thomas), 456*
- THORDARSON, O. Clinical studies on the relative incidence of congenital heart disease, 915*
- TRIER, M. Penicillin treatment of subacute bacterial endocarditis, 147*
- TROCME, P. Micronodular and reticulated appearance of the lungs during acute broncho pulmonary infection in patient with mitral disease, 914*
- TURCHETTI, A., AND SCHIROSA, G. La registrazione grafica della pressione venosa, 776*
- TURNER, LOUIS B. Asymptomatic congenital complete heart block in an Army Air Force pilot, 426
- U
- UTGTERBACK, R. A. (*See* Saccomanno, Utgterback, and Klemme), 624*
- UYEYAMA, HAJIME, KONDO, BENJAMIN, AND KAMINS, MAURICE. Arachnodactylia and cardiovascular disease—report of an autopsied case with a summary of previously autopsied cases, 580
- V
- VAN BOGAERT, A., AND VAN GENABEEK, A. Contribution to the study of electrocardiographic abnormalities of the P-Q interval, 915*
- VAN GENABEEK, A. (*See* Van Bogaert and Van Genabeek), 915*
- VANDAM, L. D. (*See* Bing, Vandam, and Gray, Jr.), 615*
- VANOSTENDE, A. (*See* Heymans, Pannier, and Vanostende), 618*
- VERBEKE, R. (*See* Heymans, Pannier, and Verbeke), 617*
- VICKERY, A. L. (*See* Woll and Vickery), 467*
- VIGRAN, I. M. (*See* Dry, Edwards, Maynard, Moe, and Vigran), 764*
- W
- WALDMAN, M. S. (*See* Kipple, Waldman, and Hall), 769*
- WALSER, A. The influence of autonomic drugs on the T waves in the exercise electrocardiogram, 147*

- WALTON, R. P., AND BRODIE, O. J. The effect of drugs on the contractile force of a section of the right ventricle under conditions of an intact circulation, 773*
- WANG, S. C., PAINTER, E. E., AND OVERMAN, R. R. The mechanism of prolonged fluorescein circulation time in experimental traumatic shock, 466*
- WARD, C. S. (See Thebaut and Ward), 770*
- WARREN, J. V. (See Nickerson, Warren, and Brannon), 619*
- WASTL, H. Observations of influence of cornsilk extract (*Stigmata maydis zcae*) on blood pressure in hypertensive rats, 922*
- WEBB, A. C. Truncus arteriosus communis persistens, 292*
- WEDDING, E. S. Actinomycotic endocarditis, 778*
- WÉGRIA, RENÉ. (See Boyle, Wégria, Cathcart, Nickerson, and Levy), 65
- WEIDEN, S. (See Krieger and Weiden), 921*
- WEINER, D. (See Friedman, Lange, and Weiner), 299*
- WEINSTEIN, B. B. (See Collins, Nelson, Jones, Weinstein, and Thomas), 456*
- WEINTRAUB, H. J., AND BISHOP, L. F. The anoxemia test for coronary insufficiency, 925*
- WEINTRAUB, HENRY J., AND BISHOP, LOUIS F., JR. Daily changing picture in a case of acute rheumatic carditis, 284
- WEISBERGER, AUSTIN S., AND FEIL, HAROLD. Lanatoside C in the treatment of persistent paroxysmal auricular tachycardia, 871
- WELIN, S., HAMBERGER, C. A., AND CRAFTOORD, C. Surgically removed foreign body embolus in the pulmonary artery, 463*
- WENDKOS, MARTIN H., AND STUDY, ROBERT S. Familial congenital complete A-V heart block, 138
- WERTMAN, MAXINE. (See Martin and Wertman), 646
- WEST, H. F. Heart disease in the case-finding program, 296*
- WEST, W. J. (See Collins, Foster, and West), 770*
- WEXLER, JACK, WHITTENBERGER, JAMES L., AND DUMKE, PAUL R. The effect of cyanide on the electrocardiogram of man, 163
- WHEELER, E. O., BRIDGES, W. C., AND WHITE, P. D. Diet low in salt (sodium) in congestive heart failure, 149*
- WHEELER, EDWIN O. (See Brown, Sampson, Wheeler, Gundelfinger, and Giansiracusa), 311
- WHITE, P. D. (See Wheeler, Bridges, and White), 149*
- WHITE, PAUL D., COHEN, MANDEL E., AND AND CHAPMAN, WILLIAM P. The electrocardiogram in neurocirculatory asthenia, anxiety neurosis, or effort syndrome, 390
- . (See Carlotti, Cohen, and White), 552
- WHITTENBERGER, JAMES L. (See Wexler, Whittenberger, and Dumke), 163
- WIDMAN, R. (See Wirtschafter and Widmann), 612*
- WIGGERS, C. J. (See Eckstein, Wiggers, and Graham), 920*
- WILBURNE, M., SURTSHIN, A., RODBARD, S., AND KATZ, L. N. Inhibition of paroxysmal ventricular tachycardia by atropine, 860
- WILENS, S. L. Bearing of general nutritional state on atherosclerosis, 461*
- WILSON, R. H., MORTAROTTI, T. G., AND DE-EDS, F. Some pharmacological properties of rutin, 932*
- WINDHOLZ, FRANK, AND GRAYSON, CHARLES E. Intrusion of aortic root into mitral orifice in hypertensive disease; radiologic observations on living persons, 180
- WINSOR, TRAVIS, ADOLPH, WILLIAM, RALSTON, WALTER, AND LEIBY, GEORGE M. Fractional circulation times using fluorescent tracer substances, 80
- WIRTSCHAFTER, Z. T., AND WIDMANN, R. The elaboration of histamine in vivo in the treatment of peripheral vascular disorders, 612*
- WOLFERTH, CHARLES C., AND LIVEZEY, MARY M. Observations on changes in ventricular complexes produced by bundle branch block with special reference to the hypothesis of electrical axis and the concept of dextrocardiogram and levocardium, 1
- WOLL, E., AND VICKERY, A. L. Primary fibrosarcoma of the heart with a vertebral metastasis, 467*
- WOLLIN, D. G. (See Johnson, Wollin, and Ross), 457*
- WOOD, J. EDWIN, JR. (See Bryant and Wood, JR.), 20
- WORTMANN, R. F. (See Davis and Wortmann), 924*

Y

- YANZ, N. (See Govier, Yanz, and Grellis), 761*
- YOHALEM, S. B. (See Gertler and Yohalem), 302*
- YOUNG, DENNISON, AND GLAUBER, JEROME J. Electrocardiographic changes resulting from acute cocaine intoxication, 272
- YOUNG, R. D., AND HUNTER, W. C. Primary myxoma of the left ventricle with embolic occlusion of the abdominal aorta and renal arteries, 466*
- YUNIEV, G. S. (See Gurvich and Yuniev), 459*

Z

- ZEMAN, F. D., AND SIEGAL, S. Monoplegia following carotid sinus pressure in the aged, 772*
- ZIMMERMAN, S. L. (See Barnett and Zimmerman), 441
- ZONDEK, H. Mixed thyroidism, 614*

SUBJECT INDEX

A

- Aberration simulating ventricular paroxysmal tachycardia, auricular fibrillation with (Gouaux and Ashman), 366
- Acidosis, diabetic, electrolyte changes and electrocardiogram in (Martin and Wertman), 646
- Actinomycotic endocarditis, 778*
- Adrenal apoplexy associated with hypertension, 458*
 - medulla, insensitivity to epinephrine in patient with functioning tumor of, 295*
- Adrenalin, increased reactivity caused by, 295*
 - producing tumor (pheochromocytoma) containing 2,300 milligrams of adrenalin, 144*
- Age groups, younger, complete heart block in (Crawford and Di Gregorio), 540
- Alkali tolerance of dog heart, 461*
- Alkaloids, veratrum, studies on; VII. Receptor areas in coronary arteries and elsewhere as revealed by use of veratridine, 769*
- Amidines, circulatory properties of iso-thioureas, guanidines, iso-ureas, and, 613*
- Aminoacetic acid, use of; specific dynamic action as means of augmenting peripheral blood flow, 298*
- Ammi visnaga in treatment of anginal syndrome, 758*
- Anaesthesia, precordial, cutaneous, in angina pectoris and coronary occlusion (experimental study), 916*
- Aneurysm, aortic, dysphagia caused by, treated by ligation of descending thoracic aorta and forward displacement of esophagus by forming new hiatus, 293*
 - root or sinus of Valsalva, syndrome of rupture of, into right atrium (Hermann and Schofield), 87
- arteriovenous, of lung, roentgen diagnosis of, 145*
 - dissecting, of aorta, 928*
 - new sign, 760*
 - related to trauma, 916*
 - with survival for three months after rupture into pleura, 759*
 - fibrous, chronic, of interventricular septum, rupture of, 148*
 - mycotic, of posterior tibial artery complicating subacute bacterial endocarditis: antemortem diagnosis confirmed by instrumental means, 764*
 - of pulmonary artery: review of literature and report of case (Deterling, Jr., and Clagett), 471
- Aneurysms, arterial, and arteriovenous fistulas, direct measurement of blood pressure within, 927*
 - syphilitic, treatment of, by cellophane wrapping, 620*
- Angina pectoris, anatomic data regarding surgical treatment of, 624*
 - and coronary occlusion, cutaneous precordial anesthesia in (experimental study), 916*
 - and what you can do for, 304 (B. Rev.)
 - thiouracil in, 148*
 - 2-thiouracil in heart failure and in, 460*
 - xanthoma tuberosum, aortic stenosis, coronary sclerosis and, 777*
 - tobacco (Bryant and Wood, Jr.), 20
- Anginal syndrome. ammi visnaga in treatment of, 758*
- Angiocardiography—comparative study with autopsy findings, 621*
- Angulation, compression and, of inferior vena cava, massive hydropericardium with (Greisman et al.), 447
- Anoxemia, myocardial and cerebral, some effects of injected cytochrome C in, in man, 143*
 - test for coronary insufficiency, 925*
- Anoxia, fulminating, electrocardiographic changes in, 300*
- Anticholinesterases, prostigmine, eserine and di-isopropylfluorophosphate, and of atropine, influence of, on central and peripheral transmission of nervous excitation, 617*
- Anticoagulants, clinical use of, 771*
 - use of, in management of acute myocardial infarction, 923*
- Antistreptolysin titer as diagnostic aid in carditis of obscure etiology, 926*
- Anuria, studies on: effect of infusion fluids and diuretics on anuria resulting from severe burns, 766*
- Anxiety neurosis, heart size in neurocirculatory asthenia, effort syndrome, or (Carloti et al.), 552
 - neurocirculatory asthenia, or effort syndrome, electrocardiogram in (White et al.), 390
- Aorta, abdominal, and renal arteries, primary myxoma of left ventricle with embolic occlusion of, 466*
 - dissecting of aneurysm of, 928*
 - new sign, 760*
 - related to trauma, 916*
 - ectatic, right-sided, 761*
 - roentgenologic diagnosis of coarctation of, 620*
 - surgical treatment of coarctation of, 620*
 - thoracic, permanent intubation of, 768*

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

- Aortic root, intrusion of, into mitral orifice in hypertensive disease; radiologic observations on living persons (Windholz and Grayson), 180
or sinus of Valsalva aneurysm into right atrium, syndrome of, rupture of (Hermann and Schofield), 87
valve, traumatic rupture of, 145*
- Arachnodactylia and cardiovascular disease—report of autopsied case with summary of previously autopsied cases (Uyeyama et al.), 580
- Army Air Force pilot, asymptomatic congenital complete heart block in (Turner), 426
- Arterial or venous thrombosis, study of normal persons and patients with: coagulation of blood in lusteroid tubes (Kadish), 212
work and pressure, influence of, on activity of cardiovascular and respiratory center, 618*
- Arteries, pulmonary, tertiary, organized emboli of, 148*
renal, primary myxoma of left ventricle with embolic occlusion of abdominal aorta and, 466*
- Arteriosclerosis, atherosclerosis and, in dogs following ingestion of cholesterol and thiouracil, 296*
cholesterol, experimental, 147*
- Arteriosclerotic heart disease, analysis of two hundred seventeen deaths due to (III); heart disease in South (Holoubek and Holoubek), 715
- Arteriovenous fistulas, pulmonary, clinical syndrome associated with, including case report of surgical cure (Burchell and Clagett), 151
- Arteritis, coronary, with fatal thrombosis due to *Salmonella choleraesuis* variety Kunzendorf (Barnett and Zimmerman), 441
- Artery and vein, coagulation thrombi in segments of, in dogs and genesis of thromboembolism, 769*
bronchial, of anesthetized dog, blood flow in 919*
coronary, single, congenital, in man (Roberts and Loubé), 188
pulmonary, aneurysm of: review of literature and report of case (Deterling, Jr., and Clagett), 471
surgically removed foreign body embolus in, 463*
- Asthenia, neurocirculatory, anxiety neurosis, or effort syndrome, electrocardiogram in (White et al.), 390
effort syndrome, or anxiety neurosis, heart size in (Carlotti et al.) 552
- Asthma, cardiac, bronchial spasm in, 462*
- Atabrine, effect of, on auricular fibrillation and supraventricular tachycardia in man, 302*
- Athero-sclerosis and arterio-sclerosis in dogs following ingestion of cholesterol and thiouracil, 296*
bearing of general nutritional state on, 461*
- Atrium, left, endocardial pockets of (Hellerstein), 751
right, syndrome of rupture of aortic root or sinus of Valsalva aneurysm into (Hermann and Schofield), 87
- Atropine, influence of anticholinesterases, prostigmine, eserine and di-isopropylfluorophosphate, and of, on central and peripheral transmission of nervous excitation, 617*
inhibition of paroxysmal ventricular tachycardia by (Wilburne et al.), 860
- Auricle above center of mitral valve, congenital muscular cord bridging walls of: asymptomatic congenital anomaly of heart (McNamara et al.), 288
left, aneurysmal dilation of, with erosion of spine, 760*
- Auricular fibrillation with aberration simulating ventricular paroxysmal tachycardia (Gouaux and Ashman), 366
muscle, isolated, of mammals, self-sustained activity in (III); studies on flutter and fibrillation, 930*
right, right ventricular and, hypertrophy of obscure origin, 144*
tachycardia, paroxysmal, of unusual type (Gendel), 722
persistent, lanatoside C in treatment of (Weisberger and Feil), 871
- A-V block, complete, variations in first heart sound in (Beard and Decherd, Jr.), 809
first and second degree, blocked (non-conducted) A-V nodal premature systoles imitating (Langendorf and Mehlman), 500
heart block, complete, familial congenital (Wendkos and Study), 138
- Ayerza's disease, 621*
syndrome, circulatory adaptations in, black cardiacs (Taquini et al.), 50

B

- Bacillus coli* endocarditis (Fletcher), 743
- Bacterial endocarditis, subacute, due to organisms highly resistant to penicillin, treatment of (Grossman et al.), 592
method of determining effective therapeutic level in treatment of, with penicillin (Schlichter and MacLean), 209
of undetermined etiology (Loewe and Eiber), 349
treatment of, with penicillin in beeswax-peanut oil: gluteal abscesses and rupture of spleen (Kennedy and Seed), 906
- Baljet reaction and pharmacodynamics of diginin (V); digitalis, 622*
on chemical evaluation of digitalis with, 914*
- Ballistocardiograph, critically damped, low frequency, and method of right atrial catheterization, studies with; cardiac output in man, 619*

- Beeswax-peanut oil, treatment of subacute bacterial endocarditis with penicillin in: gluteal abscesses and rupture of spleen (Kennedy and Seed), 906
- Beriberi heart disease, observations on (Epstein), 432
- Black cardiacs, circulatory adaptations in Ayerza's syndrome (Taquini et al.), 50
- Blood, arterial or venous, and bone marrow, comparative study of cultures of, in patients with subacute bacterial endocarditis, 767*
- coagulation of, in lusteroid tubes: study of normal persons and patients with arterial or venous thrombosis (Kadish), 212
- time of, in lusteroid tubes: study of patients receiving dicumarol (Kadish), 225
- depots, lungs as (V); functional state of vascular system in pulmonary tuberculosis, 294*
- effect of oral administration of para-aminobenzoic acid on concentration of salicylates in, 301*
- flow in bronchial artery of anesthetized dog, 919*
- peripheral, specific dynamic action as means of augmenting; use of aminoacetic acid, 298*
- through lesser circulation upon volume and elasticity of lungs, influence of alterations of, 294*
- pressure, direct measurement of, within arterial aneurysms and arteriovenous fistulas, 927*
- in hypertensive rats, observations of influence of corn-silk extract (*Stigmata maydis zae*) on, 922*
- of normal girls from three to sixteen years of age, 777*
- of rat during acute and chronic choline deficiency, 918*
- relative importance of certain variables in clinical determination of, 292*
- studies in 100 cases of coronary occlusion with myocardial infarction, 298*
- volume, circulatory corpuscle and, in case of patent ductus arteriosus before and after ligation, 916*
- of some organs (Nylín), 174
- reduced, problem of, in chronically ill patient; chronic shock, 926*
- Bone marrow, comparative study of cultures of arterial or venous blood and, in patients with subacute bacterial endocarditis, 767*
- Book reviews, 304, 779
- Bromsulphalein test, effect of circulatory factors on, in liver disease, 622*
- Bronchial spasm in cardiac asthma, 462*
- Broncho pulmonary infection, acute, micro-nodular and reticulated appearance of lungs during, in patient with mitral disease, 914*
- Bullet wounds, experimental traumatic shock produced by muscle contusion with note on effects of, 465*
- Bundle branch block, observations on changes in ventricular complexes produced by, with special reference to hypothesis of electrical axis and concept of dextrocardiogram and levocardigram (Wolferth and Livezey), 1
- syncope and, 914*
- Burns, severe, effect of infusion fluids and diuretics on anuria resulting from: studies on anuria, 766*
- C
- Capillary resistance, low, diseases associated with (Brown), 241
- Cardiac cycle, analysis of time relationships within, in electrocardiograms of normal men; V. Effect of changing heart rate upon Q-T interval and T-P interval and their respective relationships to cycle length (R-R interval) (Schlamowitz), 878
- in electrocardiograms of normal men, analysis of time relationships within; IV. Effect of position changes on relationships of Q-T and T-P intervals respectively to cycle length (R-R interval) (Schlamowitz), 702
- enlargement, rheumatic mitral valve disease without, 617*
- function test: intraventricular conduction on exercise, 465*
- metastasis, reticulum cell sarcoma with (Brick and Greenfield), 599
- murmurs, clinical features of patent ductus arteriosus with special reference to, 623*
- muscle metabolism in vitro, effect of atocopherol phosphate, digitoxin, and certain compounds related to latter on, 761*
- output in man: studies with low frequency, critically damped ballistocardiograph, and method of right atrial catheterization, 619*
- pain, high oxygen concentration under normal and increased respiratory pressure in, and in pulmonary edema, 460*
- variations of, caused by respiration, postural changes, and pressure, 767*
- roentgen and, manifestations of funnel chest, 459*
- vibrational intensity, changes in, in response to physiologic stress (Foulger et al.), 507
- Cardiacs, black, circulatory adaptations in Ayerza's syndrome (Taquini et al.), 50
- Cardio circulatory disease, recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of, 776*
- Cardioaortitis, 457*
- Cardiopatologia, 304 (B. Rev.)

- Cardiopulmonary function in four young individuals after pneumonectomy, follow-up study of, 616*
- Cardiovascular and respiratory centers, influence of arterial work and pressure on activity of, 618*
- disease, arachnodactylia and,—report of autopsied case with summary of previously autopsied cases (Ueyama et al.), 580
- diseases, 779 (B. Rev.)
- effects of sodium caprylate in cat, 769*
- manifestations of induced thyrotoxicosis, 929*
- system, lung parenchyma and, registrations of pulsations of, by Kine-densigraphy, 758*
- Carditis of obscure etiology, antistreptolysin titer as diagnostic aid in, 926*
- rheumatic, acute, daily changing picture in case of (Weintraub and Bishop, Jr.), 284
- Carotid sinus pressure, monoplegia following, in aged, 772*
- Catheterization, atrial, right, method of, studies with low frequency, critically damped ballistocardiograph, and; cardiac output in man, 619*
- heart, in investigation of congenital heart disease, 457*
- Cellophane wrapping, treatment of syphilitic aneurysms by, 620*
- Cerebral thromboangiitis obliterans, 763*
- Chemical evaluation of digitalis with Baljet reaction, 914*
- Chill and fever induced by intravenous typhoid vaccine, electrocardiogram in man during episode of (Freedberg et al.), 249
- Cholecystitis, chronic, electrocardiographic observations in, before and after surgery, 771*
- Choleraesuis*, *Salmonella*, variety Kunzendorf, coronary arteritis with fatal thrombosis due to (Barnett and Zimmerman), 441
- Cholesterol and thiouracil, atherosclerosis and arteriosclerosis in dogs following ingestion of, 296*
- arteriosclerosis, experimental, 147*
- Choline deficiency, acute and chronic, blood pressure of rat during, 918*
- Circulation during and after obstetric labor, physiologic changes in (Brown et al.), 311
- effects of intravenous injection of nicotine on (Boyle et al.), 65
- time determination, reactions of Decholin in (Norman), 740
- fluorescein, prolonged, mechanism of, in experimental traumatic shock, 466*
- fractional, using fluorescent tracer substances (Winsor et al.), 80
- thiamine, 296
- Circulatory adaptations in Ayerza's syndrome—black cardiacs (Taquini et al.), 50
- and respiratory distress from extreme position on operating table, 775*
- Circulatory—Cont'd
- blood volume of some organs (Nylin), 174
- effects of three modifications of Valsalva experiment (Rushmer), 399
- Clubbing of fingers, on etiology of (Mauer), 852
- Coagulation of blood in lusteroid tubes: study of normal persons and patients with arterial or venous thrombosis (Kadish), 212
- time of blood in lusteroid tubes: study of patients receiving dicumarol (Kadish), 225
- Coarctation of aorta, roentgenologic diagnosis of, 620*
- surgical treatment of, 620*
- Coast Guard recruits, mild rheumatic reaction in, 298*
- Cocaine intoxication, acute, electrocardiographic changes resulting from (Young and Glauber), 272
- Cold pressor test, value of, in prediction of hypertension and toxemia in pregnancy, 921*
- Compression and angulation of inferior vena cava, massive hydropericardium with (Greisman et al.), 447
- bandages, ambulatory treatment of phlebitis, thrombophlebitis, and thrombosis with, 932*
- Conduction in human heart, supernormal phase of recovery of (Mack et al.), 374
- normal and pathological aspects of, during refractory phase, 618*
- Congenital anomaly, asymptomatic, of heart: congenital muscular cord bridging walls of auricle above center of mitral valve (McNamara et al.), 288
- complete A-V heart block, familial (Wendkos and Study), 138
- heart block, asymptomatic, in Army Air Force pilot (Turner), 426
- heart disease, clinical studies on relative incidence of, 915*
- secondary hypertrophic osteoarthropathy in (Means and Brown), 262
- pulmonary stenosis with closed interventricular septum (Auerbach and Harper, Jr.), 131
- single coronary artery in man (Roberts and Loube), 188
- Congestive heart failure, comparative study on use of purified digitalis glycosides, digoxin, digitoxin, and lanatoside C, for management of ambulatory patients with (Batterman and DeGraff), 663
- Contractile force of section of right ventricle under conditions of intact circulation, effect of drugs on, 773*
- Cord, muscular, congenital, bridging walls of auricle above center of mitral valve: asymptomatic congenital anomaly of heart (McNamara et al.), 288
- Corn-silk extract (*Stigmata maydis zeae*), observations of influence of, on blood pressure in hypertensive rats, 922*

- Coronary arteritis with fatal thrombosis due to *Salmonella choleraesuis* variety Kunzendorf (Barnett and Zimmerman), 441
- artery, congenitally single, comparison of hearts with (Roberts and Loube), 200
- single, congenital, in man (Roberts and Loube), 188
- circulation in dog, 919*
- flow under conditions of hemorrhagic hypotension and shock, study of, 920*
- insufficiency, anoxemia test for, 925*
- pitressin test of (Ruskin), 569
- occlusion, cutaneous precordial anesthesia in angina pectoris and, 916*
- what you can do for angina pectoris and, 304 (B. Rev.)
- with myocardial infarction, blood pressure studies in 100 cases of, 298*
- thrombosis, paroxysmal diaphragmatic flutter with symptoms suggesting (Moore and Schoff), 889
- Corpuscle, circulatory, and blood volume in case of patent ductus arteriosus before and after ligation, 916*
- Correspondence, 306
- Cozzente del sangue, la velocita della, nella terapia, 305 (B. Rev.)
- Creatinine, exogenous, inulin and; renal filtration rates in pregnancy toxemia, 775*
- Cyanide, effect of, on electrocardiogram of man (Wexler et al.), 163
- Cycle length (R-R interval), effect of changing heart rate upon Q-T interval and T-P interval and their respective relationships to (V); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 878
- position change on relationships of Q-T and T-P intervals respectively to (IV); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 702
- Cytochrome C, injected, some effects of, in myocardial and cerebral anoxemia in man, 143*
- Cytochrome-C, variations of amount of, in myocardium and in striated muscle in human pathology, 917*
- D
- Decholin, reactions to, in circulation time determination (Norman), 740
- Dextrocardiogram and levocardigram, concept of, observations on changes in ventricular complexes produced by bundle branch block with special reference to hypothesis of electrical axis and (Wolferth and Livezey), 1
- Diabetic acidosis, electrolyte changes and electrocardiogram in (Martin and Wertman), 646
- Diaphragmatic flutter, paroxysmal, with symptoms suggesting coronary thrombosis (Moore and Schoff), 889
- Dicumarol, penicillin and, experiences with, in treatment of subacute bacterial endocarditis, 300*
- study of patients receiving: coagulation time of blood in lusteroid tubes (Kadish), 225
- treated, normal and, rats, effect of perfusion through isolated liver on prothrombin activity of blood from, 768*
- Diginin, Baljet reaction and pharmacodynamics of (V); digitalis, 622*
- Digitale et strophantines; pharmacodynamie—therapeutique, 781 (B. Rev.)
- Digitalis action, general concept of, 764*
- V. Baljet reaction and pharmacodynamics of diginin, 622*
- effect of, on fluid distribution of body, 468*
- glycosides, purified; digoxin, digitoxin, and lanatoside C, comparative study on use of, for management of ambulatory patients with congestive heart failure (Batterman and DeGraff), 663
- on chemical evaluation of, with Baljet reaction, 914*
- Digitaloids and mercurial diuretics employed in cardiology, thromboplastic properties of, 458*
- Digitoxin, certain compounds related to latter, and a-tocopherol phosphate effect of, on cardiac muscle metabolism in vitro, 761*
- digoxin, and lanatoside C, purified digitalis glycosides, comparative study on use of, for management of ambulatory patients with congestive heart failure (Batterman and DeGraff), 663
- Digoxin, digitoxin, and lanatoside C, purified digitalis glycosides, comparative study on use of, for management of ambulatory patients with congestive heart failure (Batterman and DeGraff), 663
- Di-isopropylfluorophosphate, eserine and, anticholinesterases, prostigmine, and of atropine, influence of, on central and peripheral transmission of nervous excitation, 617*
- Dilation, aneurysmal of left auricle with erosion of spine, 760*
- Diphtheria, cutaneous, with toxic myocarditis, 144*
- Diseases associated with low capillary resistance (Brown), 241
- Drugs, autonomic, influence of, on T waves in exercise electrocardiogram, 147*
- effect of, on contractile force of section of right ventricle under conditions of intact circulation, 773*
- other, comparative study of potassium thiocyanate and, in treatment of essential hypertension (Ruskin and McKinley), 691

- Dynamic action, specific, as means of augmenting peripheral blood flow; use of aminoacetic acid, 298*
- Dysentery, amebic, cardiac manifestations of toxic action of emetine hydrochloride in, 291*
- Dysphagia caused by aortic aneurysm treated by ligation of descending thoracic aorta and forward displacement of esophagus by forming a new hiatus, 293*
- E
- Ectatic aorta, right-sided, 761*
- Effort syndrome, electrocardiogram in neurocirculatory asthenia, anxiety neurosis, or (White et al.), 390
neurocirculatory asthenia, or anxiety neurosis, heart size in (Carloti et al.), 552
- Electrical axis, hypothesis of, and concept of dextrocardiogram and levocardio-gram, observations on changes in ventricular complexes produced by bundle branch block with special reference to (Wolferth and Livezey), 1
- Electrocardiogram, electrolyte and, in diabetic acidosis (Martin and Wertman), 646
esophageal, normal, 293*
exercise, influence of autonomic drugs on T waves in, 147*
in derangements of organism's water and electrolyte metabolism, 146*
in man during episode of chill and fever induced by intravenous typhoid vaccine (Freedberg et al.), 249
in neurocirculatory asthenia, anxiety neurosis, or effort syndrome (White et al.), 390
of man, effect of cyanide on (Wexler et al.), 163
- Electrocardiograms obtained from precordial positions defined by X-rays, 758*
of normal men, analysis of time relationships within cardiac cycle in; IV. Effect of position change on relationships of Q-T and T-P intervals respectively to cycle length (R-R interval) (Schlamowitz), 702
V. Effect of changing heart rate upon Q-T interval and T-P interval and their respective relationships to cycle length (R-R interval) (Schlamowitz), 878
pre-excitation, five cases with, 146*
- Electrocardiographic abnormalities of P-Q interval, contribution to study of, 915*
changes caused by hyperventilation, 299*
in early syphilis (Steiger and Edeiken), 674
in fulminating anoxia, 300*
in normal man during voluntary hyperventilation (II); studies on hyperventilation, 760*
in paroxysmal hypertension due to chromaffin adrenal tumor, 916*
- Electrocardiographic—Cont'd
resulting from adute cocaine intoxication (Young and Glauber), 272
observations in chronic cholecystitis before and after surgery, 771*
pattern of infarction of interventricular septum, extending from anterior to posterior aspect of heart (Roesler and Dressler), 817
unusual, of myocardial infarction; (Type QT₁ C₅₋₆), 460*
studies of gunshot and stab wounds of heart (Middleton), 899
study of one hundred fourteen consecutive cases of trichinosis (Solarz), 230
- Electrocardiographie, diagnostic, 780 (B. Rev.)
- Electrocardiography, fetal, technique of (Blondheim), 35
- Elektokymogram of heart and great vessel motion, interpreting (Boone et al.), 560
- Electrolyte changes and electrocardiogram in diabetic acidosis (Martin and Wertman), 646
metabolism, organism's water and, electrocardiogram in derangements of, 146*
- Elephantiasis, lymphography and, 914*
- Emboli, organized, of tertiary pulmonary arteries, 148*
- Embolism, air, cerebral, following artificial pneumothorax treatment with prolonged inhalation of oxygen, 923*
during labor, 768*
pulmonary, evaluation of, following intravascular venous thrombosis, 773*
- Emetine hydrochloride, cardiac manifestations of toxic action of, in amebic dysentery, 291*
- Emphysema, interstitial, spontaneous, of lung simulating organic heart disease (McCabe), 729
- Endocardial pockets of left atrium (Hellerstein), 751
- Endocarditis, actinomycotic, 778*
Bacillus coli (Fletcher), 743
bacterial, subacute, caused by *Streptococcus s.b.e.*, clinical manifestations of, 291*
comparative study of cultures of arterial or venous blood and bone marrow in patients with, 767*
due to organisms highly resistant to penicillin, treatment of (Grossman et al.), 592
during pregnancy, 924*
experiences with penicillin and dicumarol in treatment of, 300*
healed: report of two cases with death due to congestive heart failure, 925*
method of determining effective therapeutic level in treatment of, with penicillin (Schlichter and MacLean), 209
mycotic aneurysm of posterior tibial artery complicating: antemortem diagnosis confirmed by instrumental means, 764*
myocardial granulomas in, 293*

- Endocarditis—Cont'd
 of undetermined etiology (Loewe and Eiber), 349
 penicillin therapy of, 765*
 treatment of, 147*
 treatment of, with penicillin, 294*
 with penicillin in beeswax-peanut oil: gluteal abscesses and rupture of spleen (Kennedy and Seed), 906
 paracolon bacillus, of pulmonic valve secondary to infected polycystic kidneys, 766*
- Epinephrine, insensitivity to, in patient with functioning tumor of adrenal medulla, 295*
- Eserine and di-isopropylfluorophosphate, anticholinesterases, prostigmine, and of atropine, influence of, on central and peripheral transmission of nervous excitation, 617*
- Esophageal electrocardiogram, normal, 293*
- Esophagus, dysphagia caused by aortic aneurysm treated by ligation of descending thoracic aorta and forward displacement of, by forming new hiatus, 293*
- Extremities, intra-arterial penicillin in surgical treatment of infections of, 927*
- F
- Fallot, tetralogy of, results of preoperative studies in patients with (II); physiological studies in congenital heart disease, 615
- Familial congenital complete A-V heart block (Wendkos and Study), 138
- Feet, nongangrenous frostbite of (Holman and Pierce), 101
- Femoral vessels, method of rapid transfusion into, in patients without adequate peripheral superficial veins, 927*
- Fetal electrocardiography, technique of (Blondheim), 35
- Fever, chill and, induced by intravenous typhoid vaccine, electrocardiogram in man during episode of (Freedberg), 249
- Fibrillation, auricular, and supraventricular tachycardia in man, effect of atabrine on, 302*
 with aberration simulating ventricular paroxysmal tachycardia (Gouaux and Ashman), 366
 restoration of heart rhythm during, by condenser discharge, 459
 studies on flutter and; III. Self-sustained activity in isolated auricular muscle of mammals, 930*
- Fibrosarcoma, primary, of heart with vertebral metastasis, 467*
- Fingers, on etiology of clubbing of (Mauer), 852
- Fistulas, arteriovenous, direct measurement of blood pressure within arterial aneurysms and, 927*
 pulmonary, clinical syndrome associated with, including case report of surgical cure (Burchell and Clagett), 151
- Fluid distribution of body, effect of digitalis on, 468*
- Fluorescent tracer substances, fractional circulation times using (Winsor et al.), 80
- Flutter and fibrillation, studies on; III. Self-sustained activity in isolated auricular muscle of mammals, 930*
 case of prolonged, 458*
 diaphragmatic, paroxysmal, with symptoms suggesting coronary thrombosis (Moore and Schoff), 889
 experimental, action of artificial obstacles on, 764*
- Foreign body embolus, surgically removed, in pulmonary artery, 463*
- Fractional circulation times using fluorescent tracer substances (Winsor et al.), 80
- Frostbite, experimental, pathology of, 299*
 nongangrenous, of feet (Holman and Pierce), 101
- Funnel chest, roentgen and cardiac manifestations of, 459*
- G
- Gallop rhythm in children studied by means of calibrated phonocardiography, 465*
- Ganglia, autonomic, effects of blockade of, in man with tetraethylammonium, 295*
- Ganglionectomy, clinical studies of pharmacologic effects of tetraethyl ammonium chloride in hypertensive persons made in attempt to select patients suitable for lumbodorsal sympathectomy and, 771*
- Girls, normal, from three to sixteen years of age, blood pressures of, 777*
- Gluteal abscesses and rupture of spleen: treatment of subacute bacterial endocarditis with penicillin in beeswax-peanut oil (Kennedy and Seed), 906
- Granulomas, myocardial, in subacute bacterial endocarditis, 293*
- Great vessel, heart and, motion, interpreting electrokymogram of (Boone et al.), 560
- Growth, body, effect of patent ductus arteriosus on, 299*
- Guanidines, iso-thioureas, iso-ureas, and amidines, circulatory properties of, 613*
- Gunshot and stab wounds of heart electrocardiographic studies of (Middleton), 899
- H
- Hands of patients with rheumatic fever, observation concerning, 762*
- Heart and great vessel motion, interpreting electrokymogram of (Boone et al.), 560
 asymptomatic congenital anomaly of; congenital muscular cord bridging walls of auricle above center of mitral valve (McNamara et al.), 288

Heart—Cont'd

- block, A-V, complete, congenital, familial (Wendkos and Study), 138
- complete, congenital, asymptomatic, in Army Air Force pilot (Turner), 426
- in younger age groups (Crawford and Di Gregorio), 541
- disease, beriberi, observations on (Epstein), 432
- congenital, clinical studies on relative incidence of, 915*
- heart catheterization in investigation of, 457*
- physiological studies in; II. Results of preoperative studies in patients with tetralogy of Fallot, 615*
- secondary hypertrophic osteoarthropathy in (Means and Brown), 262
- in case-finding program, 296*
- in South; II. Statistical survey of one hundred seventeen deaths due to rheumatic heart disease (Holoubek and Holoubek), 709
- III. Analysis of two hundred seventeen deaths due to arteriosclerotic heart disease (Holoubek and Holoubek), 715
- organic, paroxysmal ventricular tachycardia with acute left ventricular failure in patient with no evidence of, 926*
- spontaneous interstitial emphysema of lung simulating (McCabe), 729
- rheumatic, liver dysfunction in, 622*
- dog, alkali tolerance of, 461*
- double rupture of, following myocardial infarction (Carroll and Cummins), 894
- electrocardiographic pattern of infarction of interventricular septum, extending from anterior to posterior aspect of (Roesler and Dressler), 817
- studies of gunshot and stab wounds of (Middleton), 899
- failure, congestive, comparative study on use of purified digitalis glycosides, digoxin, digitoxin, and lanatoside C, for management of ambulatory patients with (Batterman and DeGraft), 663
- diet low in salt (sodium) in, 149*
- report of two cases with death due to: healed subacute bacterial endocarditis, 925*
- 2-thiouracil in, and in angina pectoris, 460*
- human, supernormal phase of recovery of conduction in (Mack et al.), 374
- on case of spontaneous rupture of, with long survival, 761*
- pressures, right, recording of, in normal subjects and in patients with chronic pulmonary disease and various types of cardio circulatory disease, 776*

Heart—Cont'd

- rate, changing, effect of, upon Q-T interval and T-P interval and their respective relationships to cycle length (R-R interval) (V); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 878
- (nitroglycerine, papaverine, priscol, dibenamine hydrochloride), drug action upon myocardial epinephrine-sympathin concentration and, 763*
- rhythm, restoration of, during fibrillation by condenser discharge, 459*
- shrapnel wound of, with benign manifestations (Silverman), 419
- size in neurocirculatory asthenia, effort syndrome, or anxiety neurosis (Carlotti et al.), 552
- sound, first, in complete A-V block, variations in (Beard and Decherd, Jr.), 809
- volume, radiographic demonstration of increase in, after ingestion of litre of water, 921*
- voluntary acceleration of, in subject showing Wolff-Parkinson-White syndrome (Feil et al.), 334
- Histamine in vivo in treatment of peripheral vascular disorders, elaboration of, 612*
- Human heart, supernormal phase of recovery of conduction in (Mack et al.), 374
- Hydrochloride, emetine, cardiac manifestations of toxic action of, in amebic dysentery, 291*
- Hydropericardium, massive, with compression and angulation of inferior vena cava (Greisman et al.), 447
- Hypertension, adrenal apoplexy associated with, 458*
- and toxemia in pregnancy, value of cold pressor test in prediction of, 921*
- arterial, indications for irradiation of pituitary gland in patients with, 612*
- results of bilateral supradiaphragmatic splanchnicectomy for, 619*
- essential, comparative study of potassium thiocyanate and other drugs in treatment of (Ruskin and McKinley), 691
- considerations on surgical treatment of, by dorso-lumbar sympathectomy, 931*
- special form of, with paradoxical pharmacodynamic reactions, 917*
- experimental, physical and nervous factors in, 302*
- extensive combined thoracolumbar sympathectomy in, 775*
- menopausal, 468*
- paroxysmal, due to chromaffin adrenal tumor electrocardiographic changes in, 916*
- surgical considerations in treatment of, 773*
- with unilateral renal disease, nephrectomy for, 456*

- Hypertensive disease, intrusion of aortic root into mitral orifice in; radiologic observations on living persons (Windholz and Grayson), 180
 osteoporosis occurring during potassium thiocyanate therapy for, 932*
 pregnancy in patient with, 918*
 study of inter-action of pregnancy and, 924*
 headache treated with potassium thiocyanate, 614*
 patients, technic for testing, preoperatively, 624*
 persons, clinical studies of pharmacologic effects of tetraethyl ammonium chloride in, made in attempt to select patients suitable for lumbodorsal sympathectomy and ganglionectomy, 771*
 rats, observations of influence of corn-silk extract (*Stigmata maydis zeae*) on blood pressure in, 922*
- Hypertrophic osteoarthropathy, secondary, in congenital heart disease (Means and Brown), 262
- Hypertrophy, right ventricular and right auricular, of obscure origin, 144*
- Hyperventilation, electrocardiographic changes caused by, 299*
 pulmonary, influence of, on vasomotor reflexes of carotid sinus and on tonus of vasomotor center, 618*
 studies on; II. Electrocardiographic changes in normal man during voluntary hyperventilation, 760*
- Hypotension, hemorrhagic, and shock, study of coronary flow under conditions of, 920*
 orthostatic, post-exertional, 774*

I

- Infant and young child, salicylate intoxication in, 297*
- Infarction, myocardial, acute, use of anticoagulants in management of, 923*
 double rupture of heart following (Carroll and Cummins), 894
 high T waves in earliest stage of (Dressler and Roesler), 627
 unusual electrocardiographic pattern of; (Type QT₁ C₈₋₆), 460*
 of interventricular septum, electrocardiographic pattern of, extending from anterior to posterior aspect of heart (Roesler and Dressler), 817
 placental, possible etiologic significance of thrombosis of placental vein on mechanism of, and associated toxemia of pregnancy, 922*
- Inferior cava flow of intravascular origin, phasic changes in, 920*
- Infusion fluids and diuretics, effect of, on anuria resulting from severe burns: studies on anuria, 766*
- Insufficiency, coronary, pitressin test of (Ruskin), 569

- Intensity, vibrational, cardiac, changes in, in response to physiologic stress (Foulger et al.), 507
- Interstitial emphysema, spontaneous, of lung simulating organic heart disease (McCabe), 729
- Interventricular septum, closed, congenital pulmonary stenosis with (Auerbach and Harper, Jr.), 131
 electrocardiographic pattern of infarction of, extending from anterior to posterior aspect of heart (Roesler and Dressler), 817
- Intoxication, cocaine, acute, electrocardiographic changes resulting from (Young and Glauber), 272
- Intravenous injection of nicotine, effects of, on circulation (Boyle et al.), 65
 typhoid vaccine, electrocardiogram in man during episode of chill and fever induced by (Freedberg et al.), 249
- Intraventricular block in malnutrition and vitamin B deficiency, 297*
 conduction on exercise: cardiac function test, 465*
- Intubation, permanent, of thoracic aorta, 768*
- Inulin and exogenous creatinine; renal filtration rates in pregnancy toxemia, 775*
- Iso-thioureas, guanidines, iso-ureas, and amidines, circulatory properties of, 613*
- Iso-ureas, iso-thioureas, guanidines, and amidines, circulatory properties of, 613*

K

- Khellin, therapeutic uses of, 613*
- Kidneys, polycystic, infected, paracolon bacillus endocarditis of pulmonic valve secondary to, 766
- Kine-densigraphy, registration of pulsations of lung parenchyma and cardiovascular system by, 758*
- Kunzendorf, coronary arteritis with fatal thrombosis due to *Salmonella choleraesuis* variety (Barnett and Zimmerman), 441

L

- Labor. air embolism during, 768*
 obstetric, physiologic changes during and after (Brown et al.), 311
- Lanatoside C, digoxin, digitoxin, and, purified digitalis glycosides, comparative study on use of, for management of ambulatory patients with congestive heart failure (Batterman and DeGraff), 663
 in treatment of persistent paroxysmal auricular tachycardia (Weisberger and Feil), 871
- Leads, precordial, multiple, normal variations in (Myers et al.), 785
 V₁ and V₂, precordial, on significance of M-shaped complex in, 930*
- Leg ulcers, vascular, surgical management of, 923*

- Levocardiogram, dextrocardiogram and, concept of, observations on changes in ventricular complexes produced by bundle branch block with special reference to hypothesis of electrical axis and (Wolferth and Livezey), 1
- Ligation of vena cava, critical evaluation based on study of 212 cases, 456*
- Liver disease, effect of circulatory factors on bromsulphalein test in, 622*
- dysfunction in rheumatic heart disease, 622*
- isolated, effect of perfusion through, on prothrombin activity of blood from normal and dicumarol treated rats, 768*
- Low frequency, critically damped ballistocardiograph, and method of right atrial catheterization, studies with; cardiac output in man, 619*
- Lung, roentgen diagnosis of arteriovenous aneurysm of, 145*
- spontaneous interstitial emphysema of, simulating organic heart disease (McCabe), 729
- Lungs as blood depots (V); functional state of vascular system in pulmonary tuberculosis, 294*
- disseminated ossified nodules in, associated with mitral stenosis, 774*
- influence of alterations of bloodflow through lesser circulation upon volume and elasticity of, 294*
- micronodular and reticulated appearance of, during acute broncho pulmonary infection in patient with mitral disease, 914*
- Lusteroid tubes, coagulation of blood in: study of normal persons and patients with arterial or venous thrombosis (Kadish), 212
- study of patients receiving dicumarol (Kadish), 225
- Lymphography and elephantiasis, 914*
- M
- Malnutrition and vitamin B deficiency, intraventricular block in, 297*
- Man, effect of cyanide on electrocardiogram of (Wexler et al.), 163
- Manifestations, benign, shrapnel wound of heart with (Silverman), 419
- Menopausal hypertension, 468*
- Mercurial diuretics, digitaloids and, employed in cardiology, thromboplastic properties of, 458*
- tetany following, 921*
- Metastasis, cardiac, reticulum cell sarcoma with (Brick and Greenfield), 599
- Miocardico, infarto, forme cliniche antipiche dell, 780 (B. Rev.)
- Mitral disease, micronodular and reticulated appearance of lungs during acute broncho pulmonary infection in patient with, 914*
- orifice, intrusion of aortic root into, in hypertensive disease; radiologic observations on living persons (Windholz and Grayson), 180
- Mitral Disease—Cont'd
- stenosis and pulmonary tuberculosis, 773*
- in patients who survived age of fifty, study of, 928*
- valve, congenital muscular cord bridging walls of auricle above center of: asymptomatic congenital anomaly of heart (McNamara et al.), 288
- disease, rheumatic, without cardiac enlargement, 617*
- Monoplegia following carotid sinus pressure in aged, 722*
- Motion, heart and great vessel, interpreting electrokymogram of (Boone et al.), 560
- M-shaped complex, on significance of, in precordial Leads V₁ and V₂, 930*
- Muscle contusion, experimental traumatic shock produced by, with note on effects of bullet wounds, 465*
- striated, variations of amount of cytochrome-C in myocardium and in, in human pathology, 917*
- Muscular cord, congenital, bridging walls of auricle above center of mitral valve: asymptomatic congenital anomaly of heart (McNamara et al.), 288
- Myasthenia gravis, roentgenkymographic study of heart in, 461*
- Myocardial epinephrine-sympathin concentration and heart rate (nitroglycerine, papaverine, priscot, dibenamine hydrochloride), drug action upon, 763*
- infarction, blood pressure studies in 100 cases of coronary occlusion with, 298*
- double rupture of heart following (Carroll and Cummins), 894
- high T waves in earliest stage of (Dressler and Roesler), 627
- Myocarditis associated with acute nasopharyngitis and acute tonsillitis (Gore and Saphir), 831
- chronic isolated, 143*
- (Gore and Saphir), 827
- nonspecific, 931*
- toxic, cutaneous diphtheria with, 144*
- Myocardium, tuberculoma of (Rauchwerger and Rogers), 280
- variations of amount of cytochrome-C in, and in striated muscle in human pathology, 917*
- Myxoma, primary, of left ventricle with embolic occlusion of abdominal aorta and renal arteries, 466*
- N
- Nasopharyngitis, acute, and acute tonsillitis, myocarditis associated with (Gore and Saphir), 831
- Nephrectomy for hypertension with unilateral renal disease, 456*
- Nervous, physical and, factors, in experimental hypertension, 302*

- Neurocirculatory asthenia, anxiety neurosis, or effort syndrome, electrocardiogram in (White et al.), 390
 effort syndrome, or anxiety neurosis heart size in (Carloti et al.), 552
 Neurosis, anxiety, heart size in neurocirculatory asthenia, effort syndrome, or (Carloti et al.), 552
 neurocirculatory asthenia, or effort syndrome, electrocardiogram in (White et al.), 390
 Nicotine, effects of intravenous injection of, on circulation (Boyle et al.), 65
 Nodal premature systoles, A-V, (nonconducted), blocked, imitating first and second degree A-V block (Langendorf and Mehlman), 500
 Nodules, clinical and histopathological study of, in various rheumatic diseases, 767*
 rheumatic, in children, 294*
 Nongangrenous frostbite of feet (Holman and Pierce), 101
 Nutritional state, general, bearing of, on atherosclerosis, 461*
- O
- Obliterans, thromboangiitis, cerebral, 763*
 Obstetric labor, physiologic changes in circulation during and after (Brown et al.), 311
 Organic heart disease, spontaneous interstitial emphysema of lung simulating (McCabe), 729
 Organisms highly resistant to penicillin, treatment of subacute bacterial endocarditis due to (Grossman et al.), 592
 Orifice, mitral, intrusion of aortic root into, in hypertensive disease; radiologic observations on living persons (Windholz and Grayson), 180
 Orthostatic hypotension, post-exertional, 774*
 Osteoarthropathy, hypertrophic, secondary, in congenital heart disease (Means and Brown), 262
 Osteoporosis occurring during potassium thiocyanate therapy for hypertensive disease, 932*
- P
- Para-aminobenzoic acid, effect of oral administration of, on concentration of salicylates in blood, 301*
 Parenchyma, lung, registration of pulsations of, and cardiovascular system by Kine-densigraphy, 758*
 Paroxysmal auricular tachycardia of unusual type (Gendel), 722
 persistent, lanatoside C in treatment of (Weisberger and Feil), 871
 diaphragmatic flutter with symptoms suggesting coronary thrombosis (Moore and Schoff), 889
 tachycardia, ventricular, auricular fibrillation with aberration simulating (Gouaux and Ashman), 366
 inhibition of, by atropine (Wilburne et al.), 860
 Patent ductus arteriosus, circulatory corpuscle and blood volume in case of, before and after ligation, 916*
 clinical features of, with special reference to cardiac murmurs, 623*
 effect of, on body growth, 299*
 Pattern, electrocardiographic, of infarction of interventricular septum, extending from anterior to posterior aspect of heart (Roesler and Dressler), 817
 Penicillin and dicumarol, experiences with, in treatment of subacute bacterial endocarditis, 300*
 for scarlet fever, 616*
 in beeswax-peanut oil, treatment of subacute bacterial endocarditis with: gluteal abscesses and rupture of spleen (Kennedy and Seed), 906
 intra-arterial, in surgical treatment of infections of extremities, 927*
 method of determining effective therapeutic level in treatment of subacute bacterial endocarditis with (Schlichter and MacLean), 209
 prophylaxis in acute rheumatism, 297*
 therapy of scarlet fever, 622*
 of subacute bacterial endocarditis, 765*
 treatment of subacute bacterial endocarditis, 147*
 due to organisms highly resistant to (Grossman et al.), 592
 with, 294*
 Pericarditis, benign, acute, 621*
 Peripheral vascular disease, tetra-ethyl-ammonium as adjunct in treatment of, and other painful states, 929*
 use of radioactive sodium in study of, 624*, 765*
 venous thrombosis: preventive measures and treatment, 766*
 Pharmacodynamic reactions, paradoxical, special form of essential hypertension with, 917*
 Pheochromocytomas of suprarenal, clinical picture and treatment of, 913*
 Phlebitis, thrombophlebitis, and thrombosis, ambulatory treatment of, with compression bandages, 932*
 Phonocardiography, calibrated, gallop rhythm in children studied by means of, 465*
 Physical and nervous factors in experimental hypertension, 302*
 Physiologic stress, changes in cardiac vibrational intensity in response to (Foulger et al.), 507
 Pitressin test of coronary insufficiency (Ruskin), 569
 Pituitary gland, indications for irradiation of, in patients with arterial hypertension, 612*
 Pleura, dissecting aneurysm with survival for three months after rupture into, 759*
 Pneumonectomy, follow-up study of cardiopulmonary function in four young individuals after, 616*
 Pneumonia, rheumatic, 303*, 462*

- Pneumothorax, artificial, treatment with prolonged inhalation of oxygen, cerebral air embolism following, 923*
- Polioomyelitis, vasomotor disturbances in, with special reference to treatment with paravertebral sympathetic block, 770*
- Postural changes, respiration, and pressure, variations of cardiac pain caused by, 767*
- Potassium thiocyanate and other drugs in treatment of essential hypertension, comparative study of (Ruskin and McKinley), 691
- hypertensive headache treated with, 614
- therapy for hypertensive disease, osteoporosis occurring during, 932*
- P-Q interval, contribution to study of electrocardiographic abnormalities of, 915*
- Precordial leads, multiple, normal variations in (Myers et al.), 785
- Pregnancy and hypertensive disease, study of inter-action of, 924*
- in patient with hypertensive disease, 918*
- possible etiologic significance of thrombosis of placental vein on mechanism of placental infarction and associated toxemia of, 922*
- subacute bacterial endocarditis during, 924*
- value of cold pressor test in prediction of hypertension and toxemia in, 926*
- Pressure, variations of cardiac pain caused by respiration, postural changes, and, 767*
- Prostigmine, anticholinesterases, eserine and di-isopropylfluorophosphate, and of atropine, influence of, on central and peripheral transmission of nervous excitation, 617*
- Prothrombin activity of blood from normal and dicumarol treated rats, effect of perfusion through isolated liver on, 768*
- Pulmonary arteriovenous fistulas, clinical syndrome associated with, including case report of surgical cure (Burchell and Clagett), 151
- artery, aneurysm of: review of literature and report of case (Deterling, Jr., and Clagett), 471
- disease, chronic, recording of right heart pressures in normal subjects and in patients with, and various types of cardio circulatory disease, 776*
- edema, high oxygen concentration under normal and increased respiratory pressure in cardiac pain and in, 460*
- infarct, technique of roentgenologic demonstration of, 145*
- stenosis, congenital, with closed interventricular septum (Auerbach and Harper, Jr.), 131

Q

- Q-T and T-P intervals respectively, effect of position change on relationships of, to cycle length (R-R interval) (IV): analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 702
- interval and T-P interval, effect of changing heart rate upon, and their respective relationships to cycle length (R-R interval) (V): analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 878

R

- Radioactive sodium, use of, in study of peripheral vascular disease, 624,* 765*
- Radio-electrokymography, 758*
- Radiographic demonstration of increase in heart volume after ingestion of litre of water, 921*
- Radiologic observations on living persons: intrusion of aortic root into mitral orifice in hypertensive disease (Windholz and Grayson), 180
- Reactivity, increased, caused by adrenalin, 295*
- Refractory phase, normal and pathological aspects of conduction during, 618*
- Renal disease, unilateral, nephrectomy for hypertension with, 456*
- Resistance, capillary, low, diseases associated with (Brown), 241
- Respiration, postural changes, and pressure, variations of cardiac pain caused by, 767*
- Respiratory centers, cardiovascular and influence of arterial work and pressure on activity of, 618*
- distress, circulatory and, from extreme positions on operating table, 775*
- Reticulum cell sarcoma with cardiac metastasis (Brick and Greenfield), 599
- Rheumatic carditis, acute, daily changing picture in case of (Weinstein and Bishop, Jr.), 284
- diseases, various, clinical and histopathological study of nodules in, 767*
- fever, failure of massive salicylate therapy to suppress inflammatory reaction in, 778*
- following athletic trauma, 762*
- observation concerning hands of patients with, 762*
- heart disease, statistical survey of one hundred seventeen deaths due to (II): heart disease in South (Holoubek and Holoubek), 709
- mitral valve disease without cardiac enlargement, 617*
- nodules in children, 294*
- pneumonia, 303,* 452*
- reaction, mild, in Coast Guard recruits, 298*
- Rheumatism, acute, penicillin prophylaxis in, 297*

- Roentgen and cardiac manifestations of funnel chest, 459*
 diagnosis of arteriovenous aneurysm of lung, 145*
 Roentgenkymographic study of heart in myasthenia gravis, 461*
 Roentgenologic demonstration of pulmonary infarct, technique of, 145*
 diagnoses of coarctation of aorta, 620*
 Rupture of aortic root or sinus of Valsalva aneurysm into right atrium, syndrome of (Herrmann and Schofield), 87
 spontaneous, of heart, on case of, with long survival, 761*
 Rutin, some pharmacological properties of, 932*

S

- Salicylate intoxication in infant and young child, 297*
 therapy, massive, failure of, to suppress inflammatory reaction in rheumatic fever, 778*
 Salicylates in blood, effect of oral administration of para-aminobenzoic acid on concentration of, 301*
Salmonella choleraesuis variety Kunzendorf, coronary arteritis with fatal thrombosis due to (Barnett and Zimmerman), 441
 Salt (sodium), diet low in, in congestive heart failure, 149*
 Sangue, la velocita della cozzente del, nella terapia, 305 (B. Rev.)
 Sarcoma, reticulum cell, with cardiac metastasis (Brick and Greenfield), 599
 Scarlet fever, penicillin for, 616*
 therapy of, 622*
 Sclerosis, coronary, xanthoma tuberosum, aortic stenosis, and angina pectoris, 776*
 tuberos, with congenital tumors of heart and kidney, 292*
 Septum, interventricular, closed, congenital pulmonary stenosis with (Auerbach and Harper, Jr.), 131
 electrocardiographic pattern of infarction of, extending from anterior to posterior aspect of heart (Roesler and Dressler), 817
 rupture of chronic fibrous aneurysm of, 148*
 Shock, chronic problem of reduced blood volume in chronically ill patient, 926*
 study of coronary flow under conditions of hemorrhagic hypotension and, 920*
 traumatic, experimental, mechanism of prolonged fluorescein circulation time in, 466*
 produced by muscle contusion with note on effects of bullet wounds, 465*
 Shrapnel wound of heart with benign manifestations (Silverman), 419
 Sinus, carotid, influence of pulmonary hyper-ventilation on vasomotor reflexes of, and on tonus of vasomotor center, 618*
 of Valsalva aneurysm, syndrome of rupture of aortic root or, into right atrium (Herrmann and Schofield), 87
 Sodium caprylate, cardiovascular effects of, in cat, 769*
 South, heart disease in; II. Statistical survey of one hundred seventeen deaths due to rheumatic heart disease (Holoubek and Holoubek), 709
 III. Analysis of two hundred seventeen deaths due to arteriosclerotic heart disease (Holoubek and Holoubek), 715
 Spine, aneurysmal dilation of left auricle with erosion of, 760*
 Splanchnicectomy, supradiaphragmatic, bilateral, results of, for arterial hypertension, 619*
 Spleen, gluteal abscesses and rupture of: treatment of subacute bacterial endocarditis with penicillin in beeswax-peanut oil (Kennedy and Seed), 906
 S-T segment and T wave, observations on significance of changes of, 293*
 Stab wounds, gunshot and, of heart, electrocardiographic studies of (Middleton), 899
 Stenosis, aortic, xanthoma tuberosum, coronary sclerosis, and angina pectoris, 777*
 mitral, disseminated ossified nodules in lungs associated with, 774*
 pulmonary, congenital, with closed interventricular septum (Auerbach and Harper, Jr.), 131
Streptococcus s.b.e., clinical manifestations of subacute bacterial endocarditis caused by, 291*
 Stress, physiologic, changes in cardiac vibrational intensity in response to (Foulger et al.), 507
 Strophantines, digitale et; pharmacodynamic—therapeutique, 781 (B. Rev.)
 Suprarenal, clinical picture and treatment of pheochromocytomas of, 913*
 Surgical treatment of angina pectoris, anatomic data regarding, 624*
 Sympamina, Veritol, Sympatol: clinical and experimental studies of sympathomimetic compounds, 464*
 Sympathectomy, dorso-lumbar, considerations on surgical treatment of essential hypertension by, 931*
 for sequelae of trench feet, experiences with, 767*
 in trench foot, 463*
 lumbodorsal, and ganglionectomy, clinical studies of pharmacologic effects of tetraethyl ammonium chloride in hypertensive persons made in attempt to select patients suitable for, 771*
 thoracolumbar, extensive combined, in hypertension, 775*

- Sympathetic block, paravertebral, vasomotor disturbances in poliomyelitis, with special reference to treatment with paravertebral sympathetic block, 770*
- Sympatol, Veritol, Sympamina: clinical and experimental studies of sympathomimetic compounds, 464
- Syncope and bundle branch block, 914*
- Syndrome, Ayerza's, circulatory adaptations in,—black cardiacs (Taquini et al.), 50
 clinical, associated with pulmonary arteriovenous fistulas, including case report of surgical cure (Burchell and Clagett), 151
 effort, electrocardiogram in neurocirculatory asthenia, anxiety neurosis, or (White et al.), 390
 neurocirculatory asthenia, or anxiety neurosis, heart size in (Carlotti et al.), 552
 of rupture of aortic root or sinus of Valsalva aneurysm into right atrium (Herrmann and Schofield), 87
 Wolff-Parkinson-White, voluntary acceleration of heart in subject showing (Feil et al.), 334
- Syphilis, early, electrocardiographic changes in (Steiger and Edeiken), 674
- Systoles, premature, nodal, A-V, (nonconducted), blocked, imitating first and second degree A-V block (Langendorf and Mehlman), 500
- T
- T₁ and T₂, relations of (Goldberger), 395
- T, ondas, significado de algunas alteraciones de, 764*
- T₃, relations of T₁ and (Goldberger), 395
- T wave, observations on significance of changes of S-T segment and, 293*
 waves, high, in earliest stage of myocardial infarction (Dressler and Roesler), 627
 influence of autonomic drugs on, in exercise electrocardiogram, 147*
- Tachycardia, auricular, paroxysmal, of unusual type (Gendel), 722
 persistent, lanatoside C in treatment of (Weisberger and Feil), 871
 paroxysmal, ventricular, auricular fibrillation with aberration simulating (Gouaux and Ashman), 366
 supraventricular, auricular fibrillation and, in man, effect of atabrine on, 302*
 ventricular, paroxysmal, inhibition of, by atropine (Wilburne et al.), 860
 with acute left ventricular failure in patient with no evidence of organic heart disease, 926*
- Tetany following mercurial diuresis, 921*
- Tetra-ethyl-ammonium as adjunct in treatment of peripheral vascular disease, and other painful states, 929*
- Tetraethyl ammonium chloride, clinical studies of pharmacologic effects of, in hypertensive persons made in attempt to select patients suitable for lumbodorsal sympathectomy and ganglionectomy, 771*
- Tetraethylammonium, effects of blockade of autonomic ganglia in man with, 295*
- Tetralogy of Fallot, results of preoperative studies in patients with (II); physiological studies in congenital heart disease, 615*
- Therapeutic level, effective, method of determining, in treatment of subacute bacterial endocarditis with penicillin (Schlichter and MacLean), 209
- Thiamine circulation time, 296*
- Thiocyanate, potassium, and other drugs in treatment of essential hypertension, comparative study of (Ruskin and McKinley), 691
- Thiouracil, cholesterol and, atherosclerosis and arteriosclerosis in dogs following ingestion of, 296*
 in angina pectoris, 148*
- 2-Thiouracil in heart failure and in angina pectoris, 460*
- Thoracic aorta, descending, dysphagia caused by, aortic aneurysm treated by ligation of, and forward displacement of esophagus by forming new hiatus, 293*
- Thromboangiitis obliterans, cerebral, 763*
- Thromboembolism, genesis of, coagulation thrombi in segments of artery and vein in dogs and, 769*
 ligation of inferior vena cava in, 770*
- Thrombophlebitis on medical service of General Hospital, 300*
 phlebitis, and thrombosis, ambulatory treatment of, with compression bandages, 932*
 septic, ligation of inferior vena cava for, 772*
- Thrombosis, ambulatory treatment of phlebitis, thrombophlebitis, and, with compression bandages, 932*
 arterial or venous, study of normal persons and patients with: coagulation of blood in lusteroid tubes (Kadish), 212
 coronary, paroxysmal diaphragmatic flutter with symptoms suggesting (Moore and Schoff), 889
 fatal, coronary arteritis with, due to *Salmonella choleraesuis* variety Kunzendorf (Barnett and Zimmerman), 441
 of placental vein, possible etiologic significance of, on mechanism of placental infarction and associated toxemia of pregnancy, 922*
 venous, intravascular, evaluation of pulmonary embolism following, 773*
 peripheral: preventive measures and treatment, 766*
- Thyroidism, mixed, 614*

- Thyrotoxicosis, induced, cardiovascular manifestations of, 929*
- Time relationships within cardiac cycle in electrocardiograms of normal men, analysis of; IV. Effect of position change on relationships of Q-T and P-T intervals respectively to cycle length (R-R interval) (Schlamowitz), 702
- V. Effect of changing heart rate upon Q-T interval and T-P interval and their respective relationships to cycle length (R-R interval) (Schlamowitz), 878
- Tobacco angina (Bryant and Wood, Jr.), 20
- a-Tocopherol phosphate, digitoxin, and certain compounds related to latter, effect of, on cardiac metabolism in vitro, 761
- Tonsillitis, acute, myocarditis associated with acute nasopharyngitis and (Gore and Saphir), 831
- Toxemia, associated, of pregnancy, possible etiologic significance of thrombosis of placental vein on mechanism of placental infarction and, 922*
- hypertension and, in pregnancy, value of cold pressor test in prediction of, 921*
- pregnancy, renal filtration rates in; inulin and exogenous creatinine, 775*
- T-P interval, effect of changing heart rate upon Q-T interval and, and their respective relationships to cycle length (R-R interval) (V); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 878
- Q-T and, intervals respectively, effect of position changes on relationships of, to cycle length (R-R interval) (IV); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 702
- Tracer substances, fluorescent, fractional circulation times using (Winsor et al.), 80
- Trauma, athletic, rheumatic fever following, 762*
- dissecting aneurysm of aorta related to, 916*
- Trench feet, experiences with sympathectomy for sequelae of, 767*
- foot, sympathectomy in, 463*
- Trichinosis, electrocardiographic study of one hundred fourteen consecutive cases of (Solarz), 230
- Tricuspid valve disease, diagnosis of (Aceves and Carral), 115
- Truncus arteriosus communis persistens 292*
- Tuberculoma of myocardium (Rauchwerger and Rogers), 280
- Tuberculosis, pulmonary, functional state of vascular system in; V. Lungs as blood depots, 294*
- mitral stenosis and, 773*
- Tuberosum, xanthoma, aortic stenosis, coronary sclerosis, and angina pectoris, 777*
- Tumor, adrenal, chromaffin, electrocardiographic changes in paroxysmal hypertension due to, 916*
- functioning, of adrenal medulla, insensitivity to epinephrine in patient with, 295*
- (pheochromocytoma), containing 2,300 milligrams of adrenalin, adrenalin producing, 144*
- Tumors, congenital, of heart and kidney, tuberos sclerosis with, 292*
- Typhoid vaccine, intravenous, electrocardiogram in man during episode of chill and fever induced by (Freedberg et al.), 249
- U
- Ulcers, leg, vascular, surgical management of, 923*
- V
- Vaccine, typhoid, intravenous, electrocardiogram in man during episode of chill and fever induced by (Freedberg et al.), 249
- Valsalva experiment, circulatory effects of three modifications of (Rushmer), 399
- sinus of, aortic root or, aneurysm, syndrome of rupture of, into right atrium (Herrmann and Schofield), 87
- Valve, mitral, congenital muscular cord bridging walls of auricle above center of: asymptomatic congenital anomaly of heart (McNamara et al.), 288
- tricuspid, disease, diagnosis of (Aceves and Carral), 115
- Variations in first heart sound in complete A-V block (Beard and Decherd, Jr.), 809
- normal, in multiple precordial leads (Myers et al.), 785
- Vascular disorders, peripheral, elaboration of histamine in vivo in treatment of, 612*
- system, functional state of, in pulmonary tuberculosis; V. Lungs as blood depots, 294*
- Vasomotor disturbances in poliomyelitis, with special reference to treatment with paravertebral sympathetic block, 770*
- reflexes of carotid sinus, influence of pulmonary hyperventilation on, and on tonus of vasomotor center, 618*
- Vein, coagulation thrombi in segments of artery and, in dogs and genesis of thromboembolism, 769*
- placental, possible etiologic significance of thrombosis of, on mechanism of placental infarction and associated toxemia of pregnancy, 922*
- Veins, superficial, peripheral, adequate, method of rapid transfusion into femoral vessels in patients without, 927*
- Velocita della cozzente del sangue nella terapia, 305 (B. Rev.)

Vena cava, inferior, ligation of, 772*
 ligation of, for septic thrombophlebitis, 772*
 ligation of, in thromboembolism, 770*
 massive hydropericardium with compression and angulation of (Greisman et al.), 447
 ligation of—critical evaluation based on study of 22 cases, 456*

Venosa, pressione, registrazione grafica della, 776*

Venous, arterial or, thrombosis, study of normal persons and patients with: coagulation of blood in lusteroid tubes (Kadish), 212
 pressure, on pathological variations of, 913*

Ventricle right, effect of drugs on contractile force of section of, under conditions of intact circulations, 773*

Ventricular complexes produced by bundle branch block with special reference to hypothesis of electrical axis and concept of dextrocardiogram and levocardiogram, observations on changes in (Wolferth and Livezey), 1
 failure, left, acute, paroxysmal ventricular tachycardia with, in patient with no evidence of organic heart disease, 926*
 paroxysmal tachycardia, auricular fibrillation with aberration simulating (Gouaux and Ashman), 366
 right, and right auricular hypertrophy of obscure origin, 144*
 tachycardia, paroxysmal, inhibition of, by atropine (Wilburne et al.), 860

Veratridine, receptor areas in coronary arteries and elsewhere as revealed by use of (VII); studies on veratrum alkaloids, 769*

Veratrum alkaloids, studies on; VII. Receptor areas in coronary arteries and elsewhere as revealed by use of veratridine, 769*

Veritol, Sympamina, Sympatol: clinical and experimental studies of sympathomimetic compounds, 464*

Vertebral metastasis, primary fibrosarcoma of heart with, 467*

Vibrational intensity, cardiac, changes in, in response to physiologic stress (Foulger et al.), 507

Vitamin B deficiency, malnutrition and, intraventricular block in, 297*

W

Wolff-Parkinson-White syndrome, voluntary acceleration of heart in subject showing (Feil et al.), 334

Wound, shrapnel, of heart, with benign manifestations (Silverman), 419

Wounds, gunshot and stab, of heart, electrocardiographic studies, of (Middleton), 899

X

X-rays, electrocardiograms obtained from precordial positions defined by, 758*

Y

Younger age groups, complete heart block in (Crawford and Di Gregorio), 540

